DOES NOT CIRCULATE

Vol. 232, No. 3 **SEPTEMBER, 1956** No. 1013

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.
ESTABLISHED 1820

UNIVERSITY OF MICHIGAN
OCT 8 1956
HOSPITAL LIBRARY

Editor
RICHARD A. KERN, M.D.

Associate Editor
THOMAS M. DURANT, M.D.

Assistant Editor
CHRIS J. D. ZARAFONETIS, M.D.

Carl Bachman, Herman Beerman, Wm. L. Benedict, A. M. Bongiovanni, George E. Burch, McKeen Cattell, Frank R. Drake, G. Lyman Duff, Franklin G. Ebaugh, Noah D. Fabricant, Harry Gold, John E. Gordon, David M. Gould, Theodore H. Ingalls, N. R. Ingraham, Jr., C. G. Johnston, John G. McAfee, A. Harry Neffson, Franklin L. Payne, I. S. Ravdin, C. Thorpe Ray, Roger W. Reed, John H. Stokes, H. P. Wagener, Irving J. Wolman

Electric Activity of the Olfactory Bulb in Man. By Carl W. Sem-Jacobsen, M.D., Magnus C. Petersen, M.D., Henry W. Dodge, Jr., M.D., Quentin D. Jacks, M.D., Jorge A. Lazarte, M.D., and Colin B. Holman, M.D. 243

Cardiac Involvement in Infectious Mononucleosis. By Col. Robert J. Hoagland, MC, USA. 252

Elliptocytosis: A Study of Erythrocyte Survival Using Radioactive Chromium (CR^{51}). By R. Ross McBryde, M.D., James S. Hewlett, M.D., and Russell Weisman, Jr., M.D. 258

Ventilatory and Lung Volume Determinations in Patients with Chest Deformities. By Harry N. Iticovici, M.D., and Harold A. Lyons, M.D. 265

Fibrinogen Concentration in Various Clinical Conditions. By Samuel Losner, M.D., and Bruno W. Volk, M.D. 276

The Number of Blood Cultures Necessary to Diagnose Most Cases of Bacterial Endocarditis. By James Belli, B.S., M.S., and Burton A. Waisbren, M.S., M.D. 284

A Therapeutic Evaluation of 1-Allyl-3-Ethyl-6-Aminotetrahydropyrimidinedione (Mictine), a New Oral Diuretic. By Leonard P. Caccamo, M.D., B. H. Pringle, Ph.D., and Dale E. Hissong, B.S. 289

Effect of Carotid Sinus Denervation on Arterial Pressure Response to Tetraethylammonium Chloride in Normotensive Man. By J. W. McCubbin, M.D., W. James Gardner, M.D., and Irvine H. Page, M.D. 297

Quantitation of the Activity of Rheumatoid Arthritis. 5. A Method for Summation of the Systemic Indices of Rheumatoid Activity. By John Lansbury, M.D. 300

Progress of Medical Science

Pathology and Bacteriology—Carcinoid Tumors. By A. C. Ritchie, M.B., Ch.B (N.Z.), D.Phil. (Oxon). 311

Preventive Medicine and Epidemiology—The Community Problem in Coronary Heart Disease: A Challenge for Epidemiological Research. By David C. Miller, M.D., Fredrick J. Stare, M.D., Paul Dudley White, M.D., and John E. Gordon, M.D. 329

Physiology—Proceedings of The Physiological Society of Philadelphia, May 15, 1956. 360

Book Reviews and Notices 363

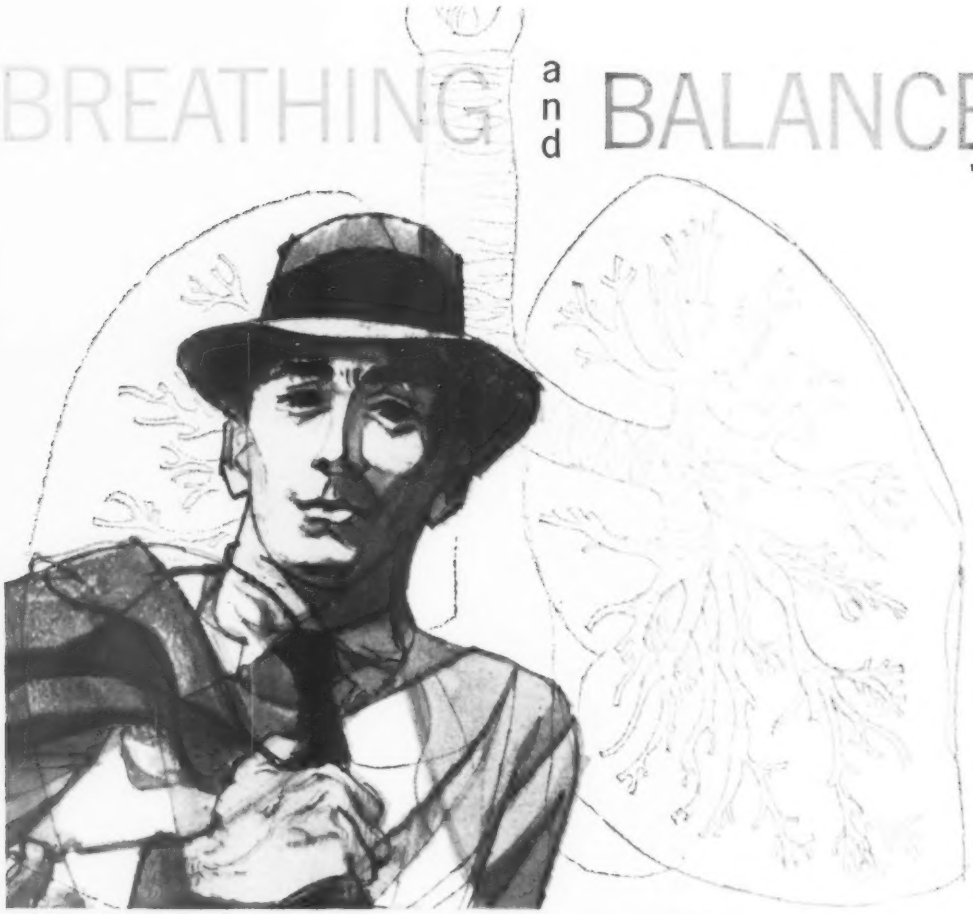
Complete contents on adv. page 8

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

Copyright, 1956, by Lea & Febiger. All Rights Reserved. Entered as second-class matter November 5, 1887 at the Post Office at Philadelphia, Pa. under the act of March 3, 1879

PUBLISHED MONTHLY. SUBSCRIPTIONS, TEN DOLLARS A YEAR

BREATHING and BALANCE



in bronchial asthma

Sterane

brand of prednisolone

one of "the best therapeutic agents now available"*

provides restoration of breathing capacity — Relief of symptoms [bronchospasm, cough, wheezing, dyspnea] is maintained for long periods with relatively small doses.*

minimal effect on electrolyte balance — "in therapeutically effective doses . . . there is usually no sodium or fluid retention or potassium loss."* Lack of edema and undesirable weight gain permits more effective therapy particularly for those with cardiac complications

Supplied: White, 5 mg. oral tablets, bottles of 20 and 100. Pink, 1 mg. oral tablets, bottles of 100. Both are deep-scored.

*Schwartz, E.: New York J. Med. 56:570, 1956.

PFIZER LABORATORIES, Brooklyn 6, New York
Division, Chas. Pfizer & Co., Inc.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

SEPTEMBER, 1956

ORIGINAL ARTICLES

ELECTRIC ACTIVITY OF THE OLFACTORY BULB IN MAN*

By Carl W. Sem-Jacobsen, M.D.

Magnus C. Petersen, M.D.

Henry W. Dodge, Jr., M.D.

Quentin D. Jacks, M.D.

Jorge A. Lazarte, M.D.

and

Colin B. Holman, M.D.

ROCHESTER STATE HOSPITAL, MAYO CLINIC AND MAYO FOUNDATION, ROCHESTER, MINNESOTA

The electric activity of the olfactory bulb in animals, especially the rabbit, has been studied extensively by Adrian and others[1]. Most of this work was carried out as acute experiments while the animal was under the influence of anesthesia. Until recently, however, little was known about the electric rhythms in the olfactory bulb of humans.

In the course of depth electrographic examination of psychotic patients, a unique opportunity presented itself for study of the electric activity of the human olfactory bulb. Since one of the reasons for these examinations was the study of the ventromedial aspects of the frontal lobe, a number of electrodes were placed in and near the olfactory bulb. As the knowledge of smell is limited, the opportunities afforded were used as fully as conditions allowed.

The examinations were limited so as not to cause the patient any additional discomfort. As far as possible, the problem was explained to the patients, several of whom became interested and gave valuable information concerning their subjective sensations.

The depth studies in all instances were made only as a preliminary examination prior to clinically indicated operations on the brain. After the electrodes had been placed, each patient was tested repeatedly over periods varying from 1 to 6 weeks.

Technique and Material. The technique used for depth electrography has been described in earlier publications[2,3]. A total of

*This investigation was supported in part (Rochester State Hospital) by research grants from the Minnesota Department of Public Welfare and the National Institute for Neurologic Diseases and Blindness.

17 patients were studied. Recordings were made from 21 implanted microelectrodes. Electrodes were placed in both bulbs in 2 patients, while 2 electrodes were placed in the same bulb in each of 2 patients. Only one electrode was placed in one of the bulbs in each of the remaining 13 patients.

Several electrodes were close together in some instances and it appeared roentgenologically as if all of them might be in the bulb. However, olfactory rhythms could be obtained from only one electrode (Fig. 1). This indicates that recordings of electric activity in the olfactory bulb can be obtained only through electrodes placed either on or in the bulb. No olfactory activity was recorded from electrodes only a few millimeters away.

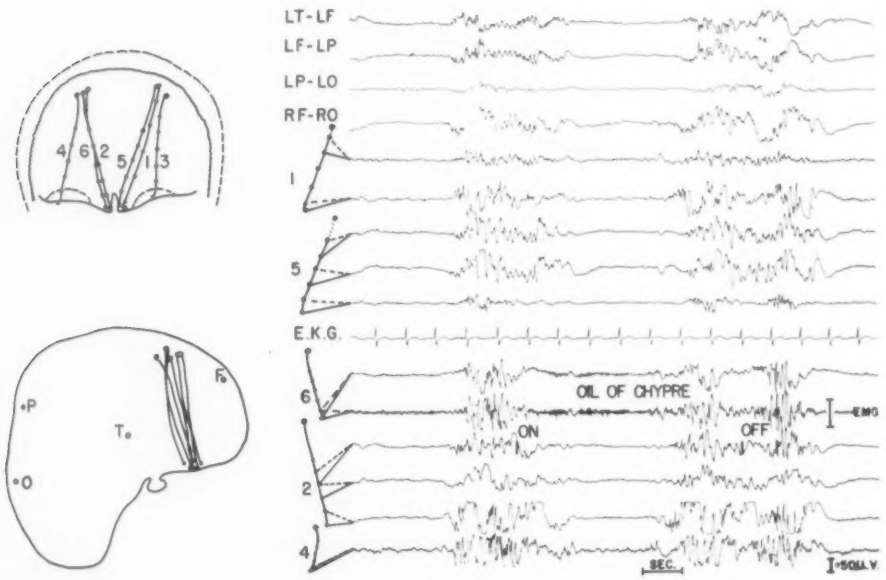


Fig. 1.—Olfactory response of patient under thiopental anesthesia. Despite close approximation of several electrodes, the olfactory response was transmitted by only one electrode.

The exact anatomic location of the electrodes placed on or in the bulb unfortunately has not been determined visually in any case. It is extremely unlikely, however, that all of them would be in identical zones. The probabilities are that they were distributed in various parts of the bulb. As yet, none of the bulbs has been examined microscopically after the electrodes were removed.

Stimulation of the nasal mucosa by odor was carried out in accordance with the technique of Elsberg[4], in which a measured amount of vapor containing the odor in question is used as a blast. Thirty milliliters of the substance emitting the odor was placed in a bottle of 530-ml. capacity. The bottle was then closed and the amount of air to be used in the blast was added under pressure. The sudden release of the pressure through a tube directed into the nostril constituted the blast. If 100 ml. was to be used, a balloon containing 50 ml. of air was connected to the bottle before the remaining 50 ml. was added to the bottle under pressure. For the test, the balloon was squeezed at the same time that the pressure was released. Generally, 100 ml. was used; for special tests, both 100-ml. and 30-ml. amounts were used separately. For other special studies, a continuous stream of air flowing at the rate of 0.5 liter to 2 liters per minute also was used.

The examinations were made while the patient was in any one of several states, namely, normally wakeful, unsedated sleep, thiopental anesthesia or ether anesthesia. So as not to cause the patient any discomfort, tests occasionally had to be terminated, thereby limiting the observations that otherwise could have been made during that particular session.

The nasal cavities were examined before,

during and after each test by an otorhinolaryngologist. If changes occurred in the nasal mucosa during a period of testing, that test was terminated.

Only a few odors were used during the early part of the work. As the studies progressed, more odors were added. Table 1 lists the odors comprising the present test battery. These odors were chosen in accordance with recommendations made in various textbooks of physiology and the availability of the odors recommended. The examinations were made in the electro-encephalographic laboratories, which have no provisions for purification of the air except forced ventilation.

TABLE 1.—ODORS USED IN ELICITING ELECTRIC ACTIVITY OF THE OLFACTORY BULB

Acetone	Carnation	Lilac
Ammonium hydroxide (10%)	Chypre	Methyl
Amorosone (synthetic musk)	Cinnamon	Neroli
Amyl acetate	Clove	2-Octanone
Anethole	Coffee	Octyl alcohol
Bay rum	Diphenylmethane	Onion
Benzaldehyde	DL Camphor	Peppermint
Benzene	Ether	Raspberry
Benzyl formate	Geranium	Sassafras
Bluebell	Hyoscyamus	Turpentine
Burnt rubber	Ionone AB	Valerian
Camphor	Lavender	Wintergreen
Cananga	Lemon	

Results. The electric activity of the olfactory bulb appears to be of two types[6,7]. The first is the resting or background activity, which is always present even though an odorous stimulus is not applied. The second is activity that is elicited as the result of stimulation of the nasal mucosa by means of various odors.

The resting or background activity was confined to a narrow band of 36 to 40 cycles per second (cps). Individual variations were encountered, however. The amplitude of these waves remained fairly constant and did not appear to be affected by respiration. Whether or not this activity is entirely intrinsic or is a response to minimal contamination of the air by odors could not be determined under existing conditions.

The electric potentials evoked in the olfactory bulb by stimulation of the nasal mucosa with vaporous odors consisted of rhythmic sinusoidal waves having a frequency of 25 to 39 cps. The frequency in some patients was slightly greater. The response to a given odor varied but little, neither in the same patient on repeated stimulation nor from patient to patient. Thus, the frequency of the response to coffee was 30 to 34 cps and that to lavender was 32 to 36 cps. However, it should be stressed that, although the various odors used evoked potentials of certain frequencies, any frequency within the frequency band might be recorded intermittently. A few of the odors used for stimulation persistently evoked responses of a wide range of frequency. Thus, the response to onion was 28 to 39 cps and that of burnt rubber was 25 to 35 cps.

Figure 2 illustrates a response to lilac that appears to be the result of two or more frequencies. This suggests that the electric response of the olfactory bulb to stimulation of the nasal mucosa by means of a given odor has a spectrum of frequencies rather than a single frequency. It should be emphasized, however, that no pure odor is known.

As described in an earlier communication[8], a state of anesthesia shifts the

frequency band for evoked potentials. With the patient under ether anesthesia, the frequency range was increased to 40 to 48 cps, while thiopental anesthesia decreased it to 17 to 25 cps. The potentials evoked by the various odors used appeared to retain in the altered frequency bands the relative position that they had before the administration of either thiopental or ether.

Vigorous blasts of certain odors on the nasal mucosa of anesthetized patients had strong arousal effects. Not only were electric potentials recorded from the olfactory bulb and from various parts of the brain affected but the clinical state of the patient was changed. Thus, a patient under deep thiopental anesthesia would begin to respond shortly after a few blasts of burnt rubber, tincture of valerian, or lilac were directed into the nostrils. Only a few odors had this strong arousal effect. Like room air, most of the odors tested had little or no arousal effect. Thus, it is conceivable that stimulation of the nasal mucosa with strong blasts of certain odors might aid in reviving patients from the effects of overdoses of barbiturates.

Some of the odors used in stimulating the nasal mucosa evoked good electric responses in the bulb. Other odors elicited only fair responses, whereas some odors produced no response at all. A few odors had an inhibitive effect, causing a flattening of the tracing.

Responses in 2 patients are illustrated in Figs. 3 and 4. In each of these figures, the odors used are listed in accordance with the degree of response recorded from one electrode. The odors giving good responses are at the top, whereas those giving poor responses are at the bottom. As long as the recordings were made from the same electrode, the order of testing the odors did not change their positions in the lists. The order of listing, according to the responses, was different from electrode to electrode when different electrodes were used. The degree of responses elicited by stimulation with nine odors in 9 patients, one of whom (Patient I) had two electrodes in the same bulb, is summarized in Table 2.

If an odor produced a good response, the amplitude of the electric potentials evoked in the bulb could be altered by varying the intensity of the stimulus.

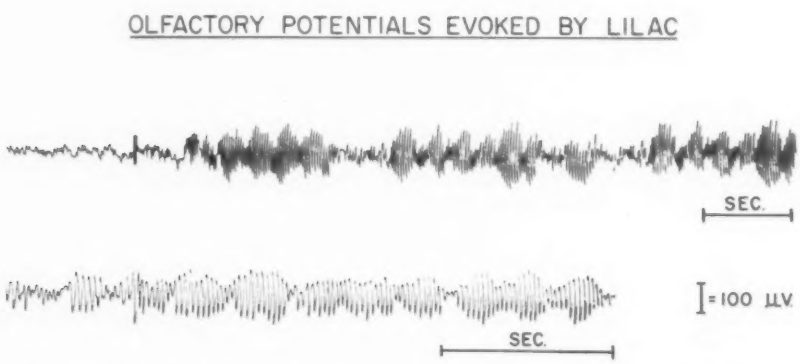


Fig. 2.—Response to lilac. Note the waxing and waning of the amplitude of the response, indicating the presence of two or more superimposed frequencies.

TABLE 2. OLFACTORY ELECTRIC RESPONSES* TO ODORS IN 9 PATIENTS

	Patients									
Odors	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I (Ant.)*	*I*
Clove	4	5	1	2	4	2	4	2	5	6
Onion	3	5	4	2	6	4	6	5	5	4
Coffee	5	4	3	2	3	3	5	4	4	6
Chypre	–	6	5	4	4	5	5	5	5	6
Wintergreen	2	4	2	2	2	3	4	5	3	3
Turpentine	3	2	2	2	3	2	3	2	3	2
Acetone	1	1	1	1	1	–	1	1	2	2
Amyl acetate	–	–	–	5	2	6	5	4	4	6
Tincture of valerian	6	5	3	2	3	–	3	–	6	6

* Grading of response: 1, flattening; 2, no response; 3, poor response; 4, fair response; 5, good response; 6, very good response.

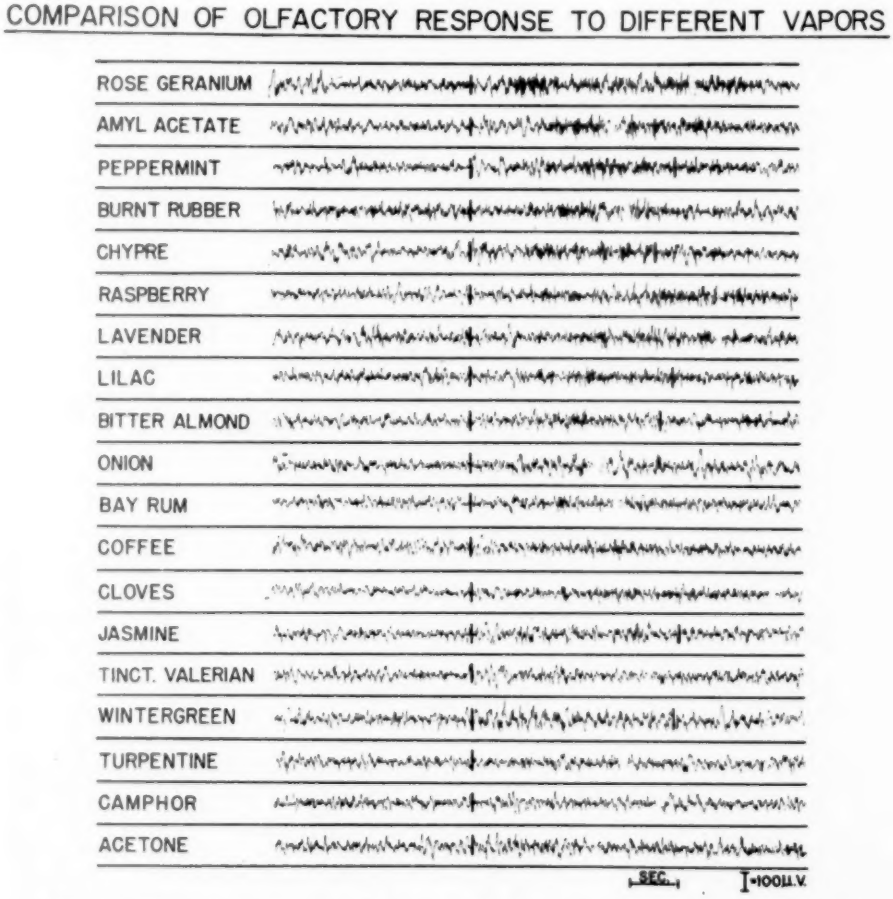


Fig. 3.—Electric responses of olfactory bulb to various odors in another patient.

Several patients from whom good responses were obtained stated that they could smell the odor only when electric responses in the bulb were elicited. Repeated tests indicated that these statements were correct. It should be emphasized that these quantitative responses were limited to odors evoking electric responses in the individual patient giving the information.

Odors giving no response might be pleasant or unpleasant. If an odor failed to evoke an electric response in the bulb, it did not matter whether the stimulating blast was strong or weak. The number of odors eliciting no response in some patients was amazingly large.

The electric response in the olfactory bulb appeared promptly when the stimulus of odor was applied to the nasal mucosa and disappeared rapidly when the stimulus was removed. The response occasionally would persist for a considerable length of time. Thus, the response in a patient showing good reaction to stimulation by means of her favorite perfume was so prolonged

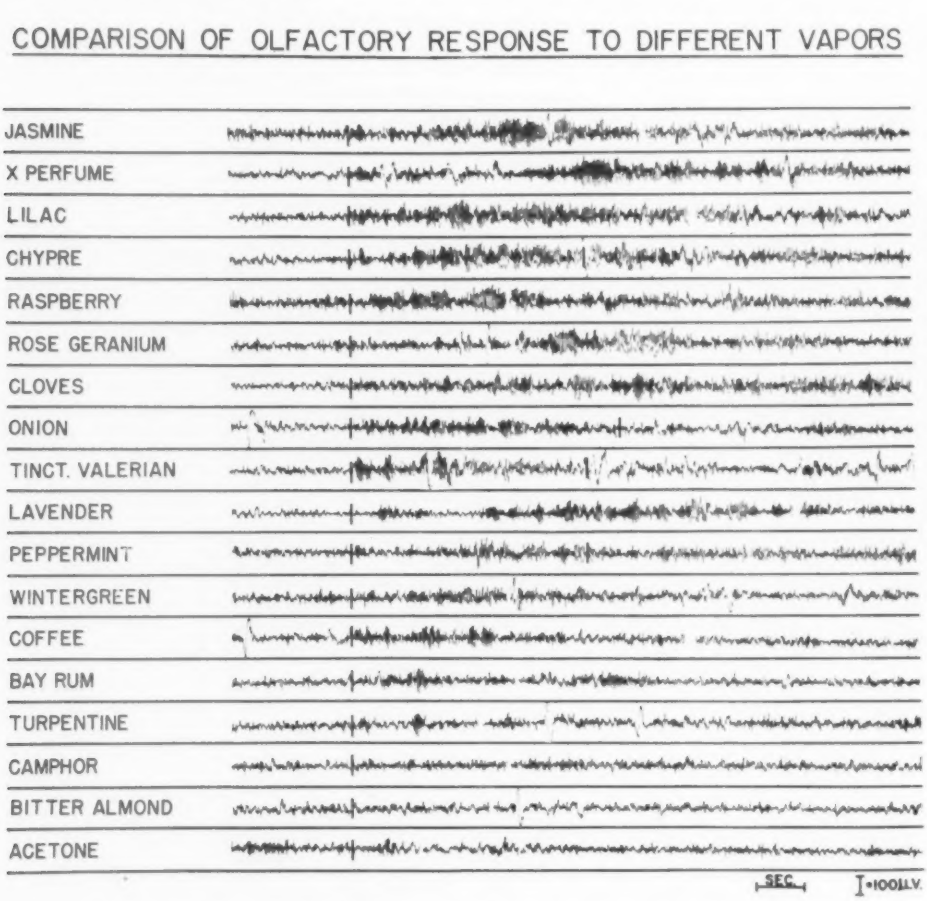


Fig. 4.—Electric responses of olfactory bulb to various odors in another patient.

that the test had to be terminated. An attempt was made on one occasion to deodorize the laboratory with a commercial deodorant. The electric responses evoked by this deodorant were so persistent that further testing was impossible for the remainder of the day.

Electric rhythms evoked by simultaneous odorous stimulation of the nasal mucosa of both nostrils of a patient having an electrode in each bulb varied in the two bulbs. The responses were neither synchronous nor of the same frequency (Fig. 5). Some of the odors that evoked good responses in one bulb produced little or no response in the other.

Another patient had two electrodes placed in the same bulb. They appeared roentgenologically to be about 5 mm. apart. The electric responses recorded from the two electrodes in this patient varied as much as did those recorded from different bulbs. The responses to various odors recorded from the two electrodes were different; they were not synchronous nor were they of the same amplitude (Table 2, Patient 1). This demonstrates that electric rhythms evoked by odors are different in various parts of the bulb.

In the earlier recordings, the background activity complicated the tracings. Use of an extra-short time constant[9] made it possible to filter out these slower rhythms and simplify analysis of the records.

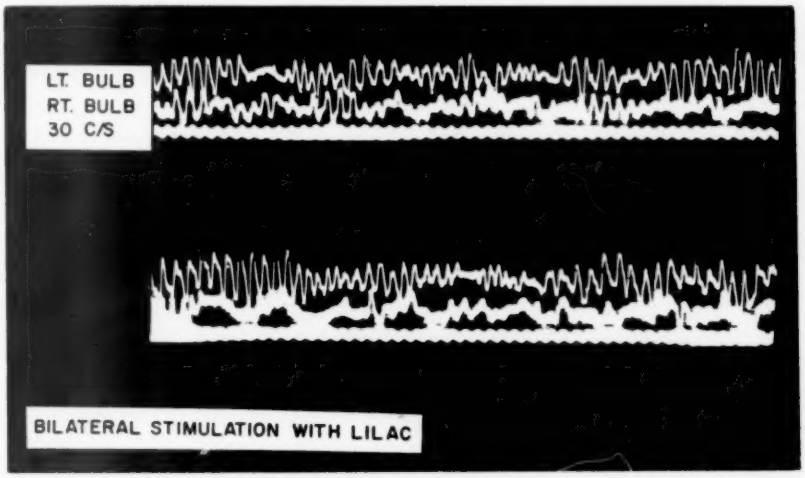


Fig. 5.—Individual electric responses to odor of each olfactory bulb, recorded by an electrode in each bulb of a patient. Note that the responses were neither synchronous nor of the same frequency.

Stimulation with some odors, especially acetone, frequently caused flattening of the tracings. Similar results have been obtained by Walsh[10] in studies employing microelectrodes. In a patient who had an extremely good response to lilac, application of strong blasts of this odor to the nostril repeatedly produced flattening of the resting or background activity for a second or so, after which the usual response appeared (Fig. 6). It appears that there was an initial blocking of the electric activity in the olfactory bulb.

Prolonged stimulation of the nasal mucosa with an odor frequently was observed to cause transitory decrease in the electric potentials evoked in the olfactory bulb. If a continuous stream of odorous vapor was used for stimullation, gradual decrease in the amplitude of the responses was noted after 10 to 100 seconds. A return toward the usual responses occurred 10 to 30 seconds after the stimulation was terminated. If another odor was used as a stimulus during the time of decreased response to one odor, the response to the second odor was immediate and of maximal amplitude.

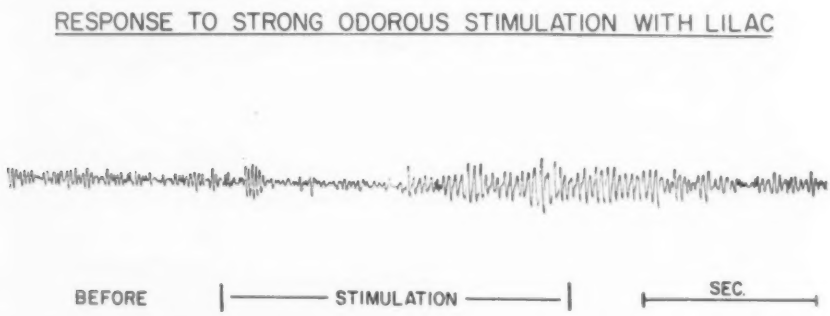


Fig. 6.—Effect of strong blasts of odor. Note flattening of background activity for a second or so, after which the usual response appeared.

Although such responses were observed frequently in the course of these studies, it cannot be stated that they are invariable. Extensive studies would be necessary to determine whether or not this type of response is common to all odors and what conditions are necessary to elicit it.

Comment and Conclusions. The findings indicate that there may be an anatomic distribution in the human olfactory bulb of individual zones, each of which responds to a limited number of odors or odor components only. A greater development of some parts of the bulb in some individuals than in others may explain why some humans and animals have a more acute sense of smell for selected odors than do others of the same species. Such an anatomic arrangement also would explain the differences in recordings obtained from the various electrodes. The data presented tend to support the theory of smell formulated by Hainer and associates[5].

The differences in frequency of the rhythms evoked by various odors need further study. An electronic analyzer capable of analyzing the frequencies reported in this study would greatly aid such investigations and might clarify the significance of the differences in frequency of the response. A greater knowledge of odors and odor components but more especially the isolation of a pure odor would be of inestimable value in such studies.

Summary. Stimulation of the nasal mucosa by odors in 17 psychotic patients evoked electric rhythms in the olfactory bulb varying in frequency from 25 to 39 cycles per second. The theory of a spectrum of electric frequency for odor in the olfactory bulb is given further support.

These electric rhythms were not synchronous either in both bulbs or in

different regions of the same bulb. The responses recorded from individual electrodes were maximal for only a limited number of odors.

Responses to the same odor recorded from various electrodes ranged from none to maximal. The responses to various odors recorded from the same electrode varied from none to maximal.

Since it is extremely unlikely that all electrodes were in the same minute regions of the bulb, the findings may indicate an anatomic distribution of individual zones in the bulb, each of which responds maximally to only a small number of odors or odor components.

REFERENCES

1. **Adrian, E. D.:** Electroencephalog. & Clin. Neurophysiol., **2**, 377, 1950.
2. **Dodge, H. W., Jr., Bickford, R. G., Bailey, A. A., Holman, C. B., Petersen, M. C.,** and **Sem-Jacobsen, C. W.:** Postgrad. Med., **15**, 291, 1954.
3. **Dodge, H. W., Jr., Petersen, M. C., Sem-Jacobsen, C. W., Sayre, G. P.,** and **Bickford, R. G.:** Proc. Staff Meet., Mayo Clin., **30**, 215, 1955.
4. **Elsberg, C. A.:** Olfactory Tests. In **Glasser, O.:** Medical Physics. Chicago: The Year Book Publishers, Inc., 1944, pp. 821–824.
5. **Hainer, R. M., Emslie, A. G.,** and **Jacobson, A.:** An Information Theory of Olfaction. Read at the "Conference on Basic Odor Research Correlation" sponsored by the New York Academy of Sciences and the American Society of Heating and Ventilating Engineers, New York, New York, April 23, 1953.
6. **Sem-Jacobsen, C. W., Bickford, R. G., Dodge, H. W., Jr.,** and **Petersen, M. C.:** Proc. Staff Meet., Mayo Clin., **28**, 166, 1953.
7. Iidem: Electroencephalog. & Clin. Neurophysiol., Suppl. **3**, 40, 1953.
8. **Sem-Jacobsen, C. W., Petersen, M. C., Lazarte, J. A., Dodge, H. W., Jr.,** and **Holman, C. B.:** Electroencephalog. & Clin. Neurophysiol., **7**, 193, 1955.
9. **Sem-Jacobsen, C. W.,** and **Kuchera, W. E.:** Unpublished data.
10. **Walsh, R. R.:** Fed. Proc., **12**, 150, 1953.

SUMMARIO IN INTERLINGUA

Activitate Electric del Bulbo Olfactori in Homines

Le stimulation del mucosa nasal per varie odores evocava in le bulbo olfactori de 17 patientes psychotic un reaction de rhythmo electric con frequentias de inter 25 e 39 cyclos per secunda. Iste observationes supporta le theoria del existentia de un spectro de frequentias electric pro odores in le bulbo olfactori.

Le observate rhythmos electric non esseva synchrone in le duo bulbos; illos esseva non mesmo synchrone in differente regiones del mesme bulbo. Le responsas registrate ab electrodos individual esseva maximal pro solmente un restringite numero de odores.

Responsas al mesme odor, registrate ab varie electrodos, variava inter nihil e valores maximal. Responsas a varie odores, registrate ab le mesme electrodo, variava equalmente inter nihil e valores maximal.

Proque il es extrememente improbabile que omne le electrodos se trovava in un mesme minute region del bulbo, nostre resultatos indica possibilemente que il existe, in le bulbo, un distribution anatomic de zonas individual que responde maximalmente a solo un reducite e specific numero de odores o de componentas de odores.

CARDIAC INVOLVEMENT IN INFECTIOUS MONONUCLEOSIS

By Colonel Robert J. Hoagland, MC, USA
CHIEF OF MEDICINE, U. S. ARMY HOSPITAL,
FORT BENNING, GEORGIA

Many case reports of cardiac complications of infectious mononucleosis have appeared, but the rate of incidence of this complication remains unknown for several reasons. First, innumerable uncomplicated cases of mononucleosis are unreported. Although many articles deal with single case reports, there are some reports of multiple cases of mononucleosis with electrocardiographic changes, but they do not deal with a large consecutive series of patients all of whom had electrocardiographic studies. Second, some cases reported as mononucleosis, but without serologic confirmation, may in fact not have been mononucleosis[6]. Third, and most important, excessive significance has been attributed to trivial electrocardiographic changes, such as lowered amplitude of T waves, resulting in diagnoses of myocardial involvement, or even myocarditis, which are open to question. A report[13] which exemplifies the latter factors will be discussed in detail below.

For these reasons, it was decided to study the electrocardiograms of 100 consecutive patients hospitalized with mononucleosis. To make certain that all patients did indeed have mononucleosis, this diagnosis was made only when clinical manifestations, blood cell changes and heterophile agglutinations characteristic of mononucleosis were present. Every patient in this series had lymphocytosis of over 50%, with presence of atypical lymphocytes, and a minimal heterophile antibody titer of 1:56 unabsorbed and 1:28 after guinea pig kidney absorption. The incidence of cardiac and other complications of mononucleosis can be reliably estimated only if the reported cases meet all three diagnostic prerequisites[7,9].

Survey of Literature. An editorial by Houck[10] on cardiac involvement in mononucleosis stated that although numerous articles have reported cardiac changes in mononucleosis, the evidence was unimpressive. He concluded that there was little to fear from heart damage due to infectious mononucleosis, and that minor electrocardiographic deviations should not cause concern to physicians or patients. Houck stated that when routine electrocardiograms were performed, the reported incidence of abnormalities was 5 to 50%. Inasmuch as our results coincided with the lower figure, it seemed worth-while to evaluate a report[12] cited by Houck which indicated that almost half of a series of mononucleosis patients had "myocarditis mononucleosa." This paper and another by Kalk and Ulbricht[13] concluded that "myocarditis mononucleosa" was frequently present in infectious mononucleosis. The latter authors reported electrocardiographic abnormalities signifying disease in 15 of 35 patients who had electrocardiograms.

The discrepancy between our findings and those of Kalk and Ulbricht are readily explained. They diagnosed mononucleosis in 56 patients in one year. However, not all had electrocardiograms, so some degree of selection may have occurred. More important, these authors included cases diagnosed as mononucleosis regardless of results of the heterophile antibody test. They

considered the test unreliable; and since negative results of the test had no diagnostic significance for them, it was not ordered in all cases. (Number of patients who had the test and titers observed were not stated.) Equally, or perhaps more, important is the debatable significance they imputed to the electrocardiographic changes. Of the 15 patients whose tracings were regarded as abnormal, 12 showed a lowered amplitude of T waves, usually in leads 2 and 3. Some of these were stated to have prolonged Q–T intervals, but the number of such patients and specific electrocardiographic data were not given. Five patients had S–T segment depressions in leads 2 and 3, but no figures are stated, so it is conjectural whether the depressions were significant. Four patients had prolonged conduction: in one instance the QRS duration was .13 sec.; the others showed slight increase of P–Q duration.

Jaffe, Field and Master[11] and Leibowitz[15] questioned the validity of the case report of Bradshaw[3] (who implied that mitral stenosis, apparent 6 weeks after recovery from mononucleosis, was a complication of the latter disease and suggested an etiologic relationship between mononucleosis and rheumatic fever). The causal relationship between his patient's mononucleosis and mitral stenosis is doubtful.

Both Jaffe and Houck re-stated the consensus of cardiologists that minor electrocardiographic alterations are without significance and that only well-defined alterations should be considered indicative of myocardial involvement. None of Jaffe's 22 cases showed significant abnormalities of T_1; and only 2 clearly showed inversion of T_4. Only one patient's electrocardiograms showed a P–R interval of over .20 second. Inasmuch as diagnoses were not in every case confirmed by positive heterophile reactions, it is uncertain whether all of his patients actually had serologically proven mononucleosis. Two of the patients with electrocardiographic deviations had heterophile reactions of only 1:8; the height of the heterophile titer was not specifically stated for the rest of the cases, with one exception. They were termed "positive." Differential white blood counts were not given.

A report of acute pericarditis associated with mononucleosis appeared in 1953[16]. Analysis of the report revealed that three authors reported on 3 patients who were seen in three different hospitals in two different cities over a period of 7 years. We can infer that acute pericarditis must be a rare complication. In a personal experience involving almost 300 patients with infectious mononucleosis, I have yet to see my first case. Bernstein[2], in a long and detailed report on mononucleosis, did not mention complicating pericarditis. Although he stated that cardiac disturbances were unusual, and despite "scantiness of these bits of evidence," he wondered "whether certain of the so-called rheumatic hearts encountered in individuals with no history of rheumatic fever or its equivalents, may not date back to a seizure of infectious mononucleosis." I believe that the passage of time and additional experience with mononucleosis have shown this speculation to be invalid.

Wechsler, Rosenblum and Sills[17] obtained electrocardiograms in 223 of 556 "epidemic" cases of mononucleosis and reported that 23% had abnormal tracings, whereas Weinstein[18], ten years later, stated that cardiac abnormalities in mononucleosis are rare. This disagreement can be resolved. First, many of the cases reported by Wechsler were, in my opinion, probably not mononucleosis. The reasons for this belief have been presented elsewhere[8]. Second, in 39 of the 53 "abnormal" electrocardio-

grams the abnormality consisted only of unusually low, iso-electric or shallowly inverted T waves in leads 2 or 3. No instances of inverted T waves in lead 1 or in the chest leads were disclosed. The authors observed that a peculiar waxing and waning of T waves was characteristic, often for a half year. This is hardly indicative of organic heart disease.

My analysis of many reported cases confirmed the opinions of Houck and of Jaffe and co-workers, who stated that nonspecific, minor alterations in the T wave are the most commonly reported abnormality. These authors re-emphasized that minor alterations of T waves may be caused by such factors as drugs, fever, increased tonus of the autonomic nervous system, electrolyte disturbance, tachycardia and by the position of the patient. It is now generally agreed that it is a mistake to interpret tracings showing only minor T-wave alterations as indicative of organic heart disease.

The report of Evans and Graybiel[5], when analyzed, supports the belief that electrocardiographic evidence of organic heart disease in mononucleosis is uncommon. These authors reported electrocardiographic changes of only 4 mononucleosis patients "in an epidemic in which upwards of 100 cases were observed." Unfortunately, it is not clear how many other patients had electrocardiographic studies. In one of the 4 cases the abnormality was limited to "progressive lowering of T_1 and T_2" (which, however, were always erect). A second patient had minimal T-wave abnormality (T_1 always erect, T_2 low and T–CF_4 diphasic in one tracing). A third patient had complicating pericarditis. In the fourth case diphasic or very shallowly inverted T waves were noted.

Histologic study of necropsy material revealed no striking myocardial changes[1,4,19]. Small, focal, interstitial infiltration of lymphocytes was the usual abnormality, one unlikely to cause clinically important heart disease. Ziegler[19] stated that the changes seen in mononucleosis are those which may be found in connection with many acute infectious diseases. He did not find cellular infiltration of the myocardium, so characteristic of the spleen, liver and other organs. Custer and Smith[4] reported on 9 necropsies of mononucleosis patients. They found no pericarditis in 8 hearts examined and in 6 cases only small infiltrates in the myocardium.

Results. After seeing many patients with mononucleosis at the U. S. Military Academy, I observed that this disease when proven serologically, was not as complicated and bizarre as one would gather from the medical literature. Therefore, in 1949, careful analysis and tabulation of data of every case of mononucleosis was begun[6]. Later, electrocardiograms became a routine procedure in the study of these patients. It soon became apparent that significant electrocardiographic abnormalities were rarely observed. Therefore, it appeared advisable to take electrocardiograms weekly lest short-lived abnormalities be missed.

TABLE 1.—INCIDENCE OF ELECTROCARDIOGRAPHIC ALTERATIONS IN MONONUCLEOSIS

No. of patients who had electrocardiographic studies	100
patients with normal tracings	95
patients with electrocardiographic alterations	5

Recording tracings in various phases of the illness was of interest because electrocardiographic abnormalities might be more common in one stage of mononucleosis than during another. Table 2 shows the distribution of electrocardiograms in relation to the course of the disease.

Electrocardiograms of only 5 of 100 consecutive patients with mononucleosis revealed any abnormalities. Two patients had minor prolongations of the P–R interval. Patient R.B. had a P–R interval of .18 sec. on the seventh day of illness. It became .20 sec. on the thirteenth day of illness, but was .18 sec. in tracings taken on the twentieth and twenty-seventh days. The first tracing of patient J.C., on the twelfth day of illness revealed a P–R interval of .21 sec. A second tracing, 8 days later disclosed an interval of .20 sec.

TABLE 2.—DISTRIBUTION OF TRACINGS ACCORDING TO STAGE OF ILLNESS

No. of electrocardiograms taken of 95 patients without abnormal tracings	158
Electrocardiograms during first week of illness	22
Electrocardiograms during second week of illness	71
Electrocardiograms during third week of illness	34
Electrocardiograms during fourth week of illness	17
Electrocardiograms after fourth week of illness	14

Patient R.K. showed complete atrioventricular heart block in a tracing taken on the thirteenth day of illness. Seven tracings, taken at about 1 to 2 week intervals for 2 months, revealed no change. He was discharged from the hospital, after 6 weeks, feeling entirely well despite his having complete atrioventricular block. Follow-up observations for over one year disclosed no change in his electrocardiogram or in his subjective state of good health.

The initial tracing, on the thirteenth day of illness, in a fourth case showed an abnormally prolonged Q–T interval (the Q–T ratio was 1.18). A second tracing, 2 weeks later was completely normal.

A fifth patient showed a flat T wave in lead 2 in an initial tracing during the second week of illness. Eight days later a second tracing showed an erect T_2. No patients showed iso-electric, diphasic or inverted T waves in leads 1 or $V_{1\text{-}6}$.

Discussion. Valvular heart disease has not proven to be a complication of mononucleosis. Acute pericarditis has occurred, but this complication is rare. In a series of almost 300 personally observed cases of mononucleosis I have not yet detected this complication, nor was it reported by Bernstein in his extensive study of mononucleosis.

That mononucleosis may affect the myocardium has been shown by necropsy reports[1,4,19]. However, the lesions described are not such as to engender concern in the clinician. Isolated case reports of electrocardiographic abnormalities observed in patients with infectious mononucleosis have given rise to an erroneous idea of the frequency of cardiac complications. Indeed, the concept that electrocardiographic changes of mononucleosis "are common" has been stated in a textbook[14].

Examination of reports of electrocardiographic alterations in mononucleosis disclosed that the diagnosis of mononucleosis was sometimes questionable. Furthermore, the electrocardiographic changes were sometimes trivial and without clinical significance. They usually consisted of lowering of amplitude or diphasic configuration or shallow inversions of T waves in leads 2 and 3 and infrequently in chest leads. Clear-cut inversion of T_1 was not described in any report available to me. P–R interval prolongation was much less frequently observed than were T-wave alterations.

In this investigation of 100 hospitalized patients with mononucleosis (limited to those with characteristic hema-

tologic and serologic changes), the incidence of significant electrocardiographic changes was only 5%. Two patients had minimal P–R interval prolongations. One patient had an increase of Q–T duration. A fourth patient showed an iso-electric T wave in lead 2. In all of these individuals electrocardiographic abnormalities disappeared during the third or fourth weeks after onset of illness. A fifth patient had complete atrioventricular heart block, which persisted during 6 weeks of hospitalization and a follow-up period of over one year. However, he had no functional impairment and no subjective, physical or roentgenographic indications of heart disease. The 95 patients without abnormalities had 158 tracings in various stages of illness.

Discrepancy between my observations and those of some authors[11,13,17] who reported a greater frequency of electrocardiographic abnormalities is attributed to three differences. This investigation is the only one, as far as I know, which included *all* cases of mononucleosis seen in a *consecutive* series. Second, mononucleosis was not diagnosed unless hematologic *and* serologic criteria were fulfilled. Third, lowered amplitude of T waves was not regarded as a significant abnormality unless at least the iso-electric position was attained. Such change was deemed significant only in leads other than lead 3 and lead V_{1-3}.

Houck stated that cardiac involvement is clinically infrequently observed and that electrocardiographic alterations were the bases for most reports of cardiac involvement in mononucleosis. He stated, or understated, that the correct interpretation of electrocardiographic alterations (consisting usually of T-wave changes) was uncertain. Inasmuch as T-wave changes can be caused by drugs, fever, functional change of the autonomic nervous system, electrolyte disturbances and other factors which do not signify organic heart disease, he recommended that electrocardiographic changes be interpreted with caution and concluded that such changes may cause too much concern in physician and patient.

Kalk and Ulbricht recommended that all mononucleosis patients have electrocardiographic study because of the frequency of "myocarditis mononucleosa," and that patients with the alterations they described should be kept in bed until these changes disappeared. However, their diagnoses of mononucleosis and their interpretations of electrocardiographic alterations are open to question.

Jaffe and co-workers recommended that when electrocardiographic abnormalities are found, the patient's activities should be restricted, and the period of convalescence should be extended, until the record returns to normal or remains stationary (in the rare cases in which the changes persist). The author believes that this policy should be confined to those patients whose electrocardiographic alterations are unquestionably significant. The significance of lowered or iso-electric T waves in leads 2 and 3 are slight.

Summary. 1. In a series of 100 consecutive hospital patients with mononucleosis who had one or more electrocardiograms only 5 showed any abnormalities; and at least one of these was of questionable significance. The changes usually disappeared before the fourth week of illness.

2. Review of many reports of electrocardiographic alterations in mononucleosis revealed that the "changes" were often not beyond the range of normal. When changes beyond normal limits were found, they were almost

always transient and usually involved T waves in lead 2.

3. Myocarditis is not a clinically recognizable feature of mononucleosis. There seems to be no more reason to fear cardiac involvement in patients with mononucleosis than physician-induced cardiac anxiety.

REFERENCES

1. **Allen, F. H.:** Am. J. Path., **23,** 463, 1947.
2. **Bernstein, A.:** Medicine, **19,** 85, 1940.
3. **Bradshaw, R. W.:** Ohio State Med. J., **27,** 717, 1931.
4. **Custer, R. P.,** and **Smith, E. B.:** Blood, **3,** 830, 1948.
5. **Evans, W. F.,** and **Graybiel, A.:** Am. J. M. Sci., **211,** 220, 1946.
6. **Hoagland, R. J.:** Am. J. Med., **13,** 158, 1952.
7. Idem: Bull. U. S. Army, Europe, **12,** 8, 1955.
8. Idem: Am. J. Med. Sci., **229,** 262, 1955.
9. **Hoagland, R. J.,** and **Gill, E. H. W.:** Deutsche med. Wchnschr., **80,** 214, 1955.
10. **Houck, G. H.:** Am. J. Med., **14,** 261, 1953.
11. **Jaffe, H. L., Field, L. E.,** and **Master, A. M.:** New York State J. Med., **48,** 1382, 1948.
12. **Kalk, H.:** Deutsche med. Wchnschr., **76,** 357, 1951.
13. **Kalk, H.,** and **Ulbricht, J.:** Ztschr. f. klin. Med., **148,** 265, 1951.
14. **Lawrence, J. S.:** Infectious Mononucleosis, *in* Textbook of Medicine, edited by **R. L. Cecil** and **R. F. Loeb,** 9th ed. Philadelphia: W. B. Saunders Co., 1955.
15. **Leibowitz, S.:** Am. J. Med., **13,** 172, 1952.
16. **Miller, H., Uricchio, J. F.,** and **Phillips, R. W.:** New England J. Med., **249,** 136, 1953.
17. **Wechsler, H. F., Rosenblum, A. H.,** and **Sills, C. T.:** Ann. Int. Med., **25,** 236, 1946.
18. **Weinstein, L.:** Mod. Concepts Cardiovas. Dis., **23,** 229, 1954.
19. **Ziegler, E. E.:** A.M.A. Arch. Path., **37,** 196, 1944.

SUMMARIO IN INTERLINGUA

Involvimento Cardiac in Mononucleosis Infectiose

1. In un serie de 100 consecutive patientes hospitalisate con mononucleosis qui habeva un o plure electrocardiogrammas, solmente 5 monstrava ulle anormalitate, e in al minus un de iste casos le anormalitates esseva de signification questionabile. Usualmente le alterationes dispareva ante le quarte septimana del morbo.

2. Un revista de numerose reportos de alterationes electrocardiographic in mononucleosis revelava que ille "alterationes" remaneva frequentemente intra le limites de lo que es normal. Quando alterationes excedente le limites del norma esseva trovate, illos esseva quasi semper de natura transiente e involveva usualmente undas T in derivation 2.

3. Myocarditis non es un clinicamente recognoscibile characteristica de mononucleosis. Il pare que le sol base pro timer involvimento cardiac in patientes con mononucleosis es le anxietate inducite per le medico.

ELLIPTOCYTOSIS: A STUDY OF ERYTHROCYTE SURVIVAL USING RADIOACTIVE CHROMIUM (CR^{51})*

By R. Ross McBryde, M.D.**
MONTGOMERY, ALABAMA

James S. Hewlett, M.D.
STAFF, DEPARTMENT OF MEDICINE, CLEVELAND CLINIC

AND

Russell Weisman, Jr., M.D.
SENIOR INSTRUCTOR IN MEDICINE, SCHOOL OF MEDICINE, WESTERN RESERVE UNIVERSITY

(From The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio)

Elliptocytosis is a hereditary anomaly of the red blood cells characterized by the presence of oval and elliptical cells in the peripheral blood. The condition is usually benign and not associated with anemia, but a small percentage of patients exhibit signs and symptoms of a hemolytic process.

A review of the literature reveals relatively few reports on red cell survival time in this condition[17]. Strumia and associates[17] using the radiochromate (Cr^{51}) method recently reported a study of the autosurvival of elliptocytes in a splenectomized subject. They reported that the survival was much longer in the splenectomized patient than in a normal recipient transfused with the patient's red cells. Our case offered an excellent opportunity to study erythrocyte survival using the sodium chromate (Cr^{51}) method, in a patient with elliptocytosis who had not had a splenectomy.

Case Report. A 53-year-old Negro housewife was initially examined on November 16, 1954, because of a "gnawing" epigastric pain of one year's duration. The pain occurred almost daily, and was relieved by food. During the month preceding examination she had lost 10 pounds in weight. Hypertension was known to have been present for 15 years. During the year prior to examination she had received penicillin injections once a week for 9 months, presumably because of a positive serologic test for syphilis. The patient stated that she had no knowledge of a previous anemia.

There was a family history of hypertension but none of anemia. The patient's parents were dead but her three siblings, two sisters and one brother, were living and well. A blood sample from one of her sisters, the only available sibling, was examined and showed no erythrocyte abnormality.

Physical examination revealed a well-developed woman who did not appear to be ill. The conjunctivae were slightly pale, but there was no jaundice. The pupils reacted normally and ophthalmoscopic examination revealed no significant changes. The lungs were clear; auscultation of the heart disclosed a soft grade 2 apical systolic murmur. Abdominal examination revealed no tenderness or masses, and the spleen was not palpable. Neurologic examination was negative.

Examination of the blood repeatedly over a 6-month period disclosed that the red blood

*This study was supported in part by a grant from the U. S. Public Health Service, H–1263C. The radioactive chromium used in this investigation was supplied by the Abbott Laboratories on authorization from the Isotopes Division, U. S. Atomic Energy Commission.

**Former Fellow in Clinical Pathology, Cleveland Clinic; present address, 345 S. Ripley Street, Montgomery, Alabama.

cell count ranged from 2,800,000 to 3,500,000 per c. mm., the hemoglobin from 8.4 to 10.0 gm. per 100 ml., and the hematocrit reading from 32 to 34%. The mean corpuscular volume averaged 104 cubic microns (range 98 to 110), the mean corpuscular hemoglobin concentration 28% (range 26 to 29), and the reticulocytes 1.3% (range 1 to 1.9). The leukocyte count ranged from 4,750 to 9,600 per c. mm., with a normal differential count. Examination of stained peripheral blood films repeatedly over a period of 6 months revealed striking abnormalities in red cell morphology with numerous ovalocytes, elliptocytes, microspherocytes and cellular fragments (Fig. 1). No target cells were present, and hypochromia was not conspicuous.

A differential count of the erythrocytes was done and the results are presented in Table 1.

Studies of osmotic fragility gave the following results (corrected to pH 7.4):

Per Cent Hemolysis	*NaCl (gm./100 ml.)*	*Normal Range NaCl (gm./100 ml.)*
1	0.63	0.44—0.49
5	0.53	0.42—0.49
10	0.51	0.40—0.46
25	0.47	0.39—0.45
50	0.44	0.38—0.44
75	0.42	0.36—0.41
90	0.39	0.34—0.38

The erythrocyte mechanical fragility was 8.5% (normal 5% or less). Direct and indirect antiglobulin (Coombs) tests were negative, and no erythrocyte antibodies were demonstrated either absorbed on the patient's cells or in the serum. The Donath-Landsteiner and acid hemolysin tests were negative. Alkali-resistant hemoglobin determined by the method of Singer, Chernoff and Singer[16] was within normal limits. The red cells did not sickle, and electrophoretic analysis of the hemoglobin by the paper strip method, using barbiturate buffer at pH of 8.6, revealed a single component with the mobility of normal hemoglobin. A bone marrow examination revealed normoblastic erythroid hyperplasia with a myeloid-erythroid ratio of 1.7 to 1.

Blood chemistry measurements disclosed a fasting blood sugar of 88 mg., urea 21 mg., and serum uric acid of 2.8 mg. per 100 ml. The total serum protein was 8.5 gm. per 100 ml. with an albumin-globulin ratio of 5.2 to 3.3. Tiselius protein studies revealed no significant abnormality. The blood Wassermann and Kahn reactions were 4 plus. The cerebrospinal fluid contained no cells, and gave negative Wassermann, Kahn, and colloidal gold reactions. A test for lupus erythematosus was negative. Two stool examinations were negative for parasites and occult blood. A gastric analysis following injection of histamine revealed 80 degrees of free hydrochloric acid. The basal metabolic rate was + 8%. A routine urinalysis was negative, and the urea clearance rate was normal.

A roentgenogram of the thorax showed slight left ventricular enlargement. Roentgen studies of the stomach and duodenum revealed a deformity of the first portion of the duodenum with an associated small pseudodiverticulum. A barium enema and small bowel series were normal. An electrocardiogram was within normal limits.

The patient was treated with a modified ulcer program and the epigastric discomfort disappeared. Based on the morphologic abnormality of the red cells, a diagnosis of elliptocytosis was made. Because of the macrocytosis, the patient was given an adequate therapeutic trial with parenteral vitamin B_{12} and oral folic acid. There was no reticulocyte response and no subsequent improvement of the anemia. In addition iron therapy was given by mouth on an empirical basis for 2 months but without improvement of the anemia. Splenectomy was recommended, but in the absence of symptoms was refused by the patient.

Red cell survival studies were carried out with the radioactive chromium (Cr^{51}) method. The technique of tagging the erythrocytes with Cr^{51} was that described by Ebaugh, Emerson and Ross[5]. The study was performed by reinjecting 50 ml. of the patient's own blood, after labeling with approximately 80 microcuries of sodium chromate (Cr^{51}). Figure 2 demonstrates impairment of the erythrocyte survival with a half-life[14,21] of 18.5 days as compared with

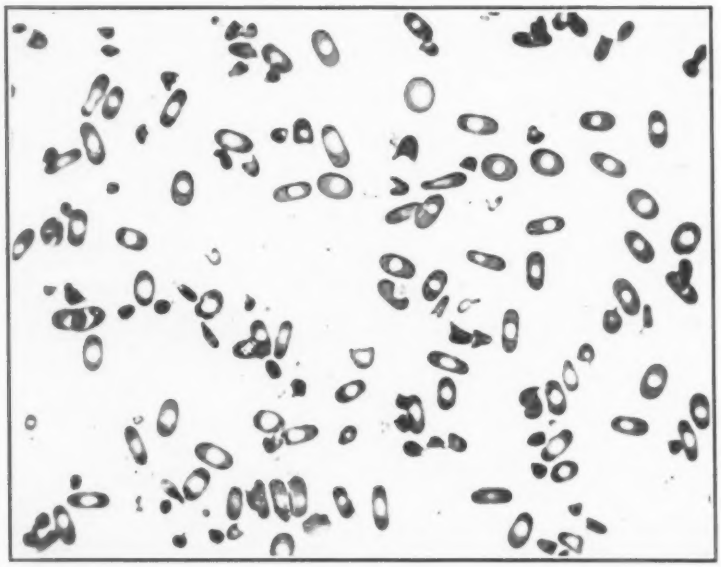


Fig. 1.—Photomicrograph of a sample of the patient's peripheral blood revealing ovalocytes, elliptocytes, microspherocytes and fragmented forms. × 540.

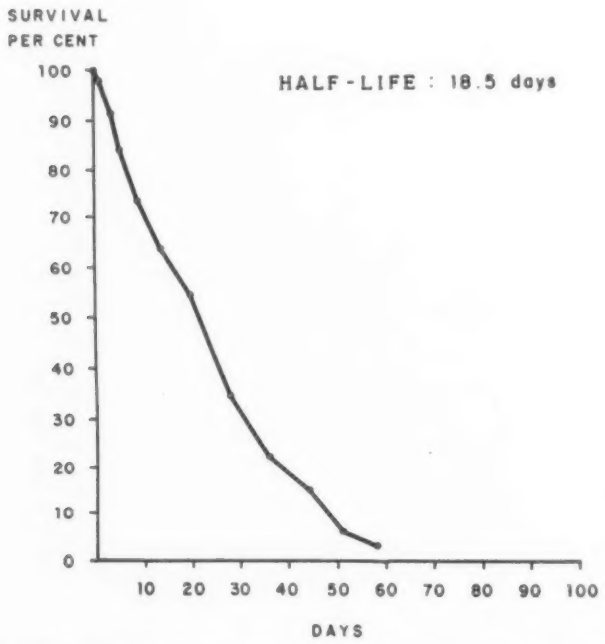


Fig. 2.—Cr^{51} red cell autosurvival curve in a patient with elliptocytosis.

the half-life for normal red cells of 33.1 ± 3.2.

Discussion. A study of this patient's blood demonstrated ovalocytes, elliptocytes, and microspherocytes. In addition, an increased osmotic and mechanical fragility, and a shortened survival time of the erythrocytes were found. Although the familial nature of this patient's disease could not be definitely established, the severity of the erythrocyte deformity strongly suggested that the elliptocytosis was of the hereditary rather than of the "symptomatic" type. The presence of microspherocytes and the increased osmotic fragility does not necessarily indicate increased saline osmotic fragility[3,4,6,10,12,13]. It is probable, according to Dacie[3], that evidence of hemolysis will always be found in those cases where spherocytes occur. It has been demonstrated that not only are the microspherocytes osmotically more fragile, but also that the erythrocyte fragments have an increased osmotic fragility[4]. Therefore, based on Dacie's observations, approximately 40% of our patient's red cells might be considered potentially more fragile than normal (Table 1, Fig. 1), and thus perhaps might be destroyed more rapidly than the other red cells in the population. However, the erythrocyte survival study in our patient showed a survival curve which would not suggest a double population in which a portion of the red cells were being destroyed more rapidly than other cells, as might occur if the microspherocytic and fragmented forms were the sole cause of the hemolytic process. The survival curve indicated rather that the entire red cell population had a diminished life-span and that all cells were destroyed at essentially the same rate. Accordingly, microcytic elements may have contributed to the hemolysis but they were not the entire explanation for the anemia.

TABLE 1.—DIFFERENTIAL ERYTHROCYTE COUNT OF PERIPHERAL BLOOD

	Type	*Percentage*
I	Round cells	3.7
IIa	Oval cells	15.6
IIb	Microcytic oval cells	2.0
IIIa	Elliptical cells	23.1
IIIb	Microcytic elliptical cells	4.5
IVa	Cigar-shaped cells	8.8
IVb	Microcytic cigar-shaped cells	0.5
V	Microspherocytes	16.0
VI	Cellular fragments (schizocytes?)	25.8

an admixture of elliptocytosis with hereditary spherocytosis trait. According to Dacie[3], spherocytosis and microcytosis as seen in hereditary elliptocytosis are the result of an increased expressivity of the gene for elliptocytosis. Others[13] are of the opinion that spherocytosis is secondary to erythrocytic fragmentation. In our patient other causes of "symptomatic" ovalocytosis were excluded, such as pernicious anemia, thalassemia, hypochromic anemia of Rundles and Falls[15], and the abnormal hemoglobin diseases.

Although blood from our patient had an increased saline osmotic fragility, evidence in the literature suggests that a hemolytic anemia in elliptocytosis may occur with either a normal or an

In hemolytic disorders, anemia usually occurs only when the total life-span of the erythrocyte is diminished to 15 to 20 days, the normal marrow be-

ing able to compensate to this degree by increasing the rate of erythropoiesis approximately seven times the normal output[2]. If this is true, the red cell survival time in our patient does not appear to be sufficiently shortened to produce anemia. It is difficult to explain, therefore, why this patient with a bone marrow which showed erythroid hyperplasia could not maintain a normal hemoglobin level when the erythrocyte survival time was roughly one-half normal.

In elliptocytosis associated with hemolytic anemia, the life-span of the elliptocyte is of considerable significance. The first attempts to measure the elliptocyte survival time were carried out by transfusing blood from patients with elliptocytosis into normal recipients with subsequent determination of the percentage of abnormal cells remaining in the blood by observing them visually or photomicrographically[7,9,20]. Studies based on this method suggested that elliptocyte survival time was significantly shortened. The accuracy of the method is still in doubt. Trinick[19] apparently was the first to study survival of elliptocytes by the Ashby technique of differential agglutination. He found an erythrocyte life-span of 100 to 110 days in a patient with 90% elliptocytes. Berlin and Hedenstedt[1] transfused blood from a patient with elliptocytosis into 2 normal recipients and studied the red cell survival by both the photomicrographic and Ashby methods simultaneously in each recipient. With the photomicrographic method one-half of the elliptocytes could no longer be distinguished after 15 to 20 days, whereas by the Ashby method the elliptocytes were eliminated from the recipient's circulation in a linear fashion and 50% of the transfused cells could still be observed after 47 days. They explained this discrepancy by assuming that the elliptocytes gradually became round when transfused into a normal recipient. This hypothesis has not been confirmed. Letman[11] demonstrated that elliptical cells disappeared very rapidly from the circulation, but found the survival curves by the morphologic and by the Ashby techniques were not parallel. He hypothesized that more rapid destruction of the most elliptical cells accounted for the discrepancy.

Recently Motulsky *et al.*[13] reported that red cell survival times, as determined by the differential agglutination method, were 117, 45, and 103 days respectively, in 3 patients with elliptocytosis. In 2 of the patients they compared the results obtained by the Ashby method with visual counts of the elliptocytes and found fairly close agreement between the two techniques. The patient having the shortest survival time (45 days) had a mild compensated hemolytic process.

Hurley and Weisman[8] by a modified Ashby technique observed a survival time of approximately 60 days, when blood from a nonanemic donor with elliptocytosis was transfused into a normal recipient. Strumia *et al.*[17] using parallel survival study with chromium-tagged cells (autosurvival in a splenectomized patient and survival in a normal recipient) demonstrated a much shorter survival time in the normal recipient than in the splenectomized patient. Apparently, as Strumia points out, the normal recipient's spleen played an active part in removal of the more altered cells from the circulation.

It thus appears that elliptocytes may have a normal survival as observed in most instances, or a shortened survival which may or may not be associated with anemia.

It is tempting to hypothesize that those patients showing short survival of the elliptocytes are homozygous for the elliptocytosis trait, while those

showing a normal rate are heterozygous. This hypothesis cannot be tested in the present instance since the patient's parents are dead. If the hypothesis of homozygosity and heterozygosity is true, elliptocytosis is similar to other hereditary hemolytic anemias such as sickle cell anemia. A case of severe hemolytic elliptocytosis in a patient presumably homozygous for the trait (both of the parents carried the trait for elliptocytosis and were nonanemic), has been reported by Wyandt, Bancroft, and Winship[23]. On the other hand, cases of hemolytic elliptocytosis have been reported which were heterozygous[4,10], only one parent carrying the elliptocytosis trait. Therefore, the explanation for the anemia and short survival time on the basis of homozygosity alone is untenable. Perhaps the condition is comparable, as Motulsky *et al.*[13] suggest, to the minor forms of thalassemia where survival time is normal in some patients heterozygous for the thalassemia trait, while in others, also heterozygous for the trait, survival time is mildly to moderately shortened and there is a variable hematologic picture. According to Motulsky *et al.*[13], the variable hematologic picture seen in heterozygous carriers of thalassemia or elliptocytosis is usually explained by postulating incomplete penetrance of the respective gene. It is also possible that the association of the elliptocytosis trait with some as yet unrecognized abnormality may be responsible for the anemia in some cases. In this regard it is interesting to note that Strumia *et al.'s*[17] patient with anemia had thalassemia minor as well as elliptocytosis, and Dacie[3] gives two examples of elliptocytosis associated with superimposed blood disease, one patient having paroxysmal nocturnal hemoglobinemia, the other an autoimmune hemolytic anemia. Although the patient presented here had no evidence of thalassemia minor or any other associated disease, this possibility cannot be entirely excluded.

Summary. A case of elliptocytosis with an associated uncompensated hemolytic process, and a decreased erythrocyte autosurvival time (half-life of 18.5 days) measured by the sodium chromate (Cr^{51}) method is presented. The literature on red cell survival times in elliptocytosis has been reviewed. The present case of elliptocytosis is the first reported with a proved short autosurvival time.

REFERENCES

1. **Berlin, R.,** and **Hedenstedt, S.:** Acta med. scandinav., **143,** 273, 1952.
2. **Crosby, W. H.,** and **Akeroyd, J. H.:** Am. J. Med., **13,** 273, 1952.
3. **Dacie, J. V.:** The Hemolytic Anemias. New York: Grune & Stratton, Inc., p. 536, 1954.
4. **Dacie, J. V., Mollison, P. L., Richardson, N., Selwyn, J. G.,** and **Shapiro, L.:** Quart. J. Med., **22,** 79, 1953.
5. **Ebaugh, F. G., Jr., Emerson, C. P.,** and **Ross, J. F.:** J. Clin. Invest., **32,** 1260, 1953.
6. **Giffin, H. Z.,** and **Watkins, C. H.:** Tr. Assn. Am. Phys., **54,** 355, 1939.
7. **Hedenstedt, S.:** Acta chir. scandinav. (supp. 128), **95,** 1, 1947.
8. **Hurley, T. H.,** and **Weisman, R., Jr.:** J. Clin. Invest., **33,** 835, 1954.
9. **Kirkegaard, A.,** and **Larsen, K.:** Acta med. scandinav., **110,** 521, 1942.
10. **Larsen, T. H.:** Nord. Med., **34,** 925, 1947.
11. **Letman, H.:** Acta med. scandinav., **151,** 41, 1955.
12. **Mason, V. R.:** In Downey, Hal (Editor), Handbook of Hematology, Vol. 3, New York: Paul B. Hoeber, Inc., p. 2351, 1938.
13. **Motulsky, A. G., Singer, K., Crosby, W. H.,** and **Smith, V.:** Blood, **9,** 57, 1953.
14. **Necheles, T. F., Weinstein, I. M.,** and **LeRoy, G. V.:** J. Lab. & Clin. Med., **42,** 358, 1953.
15. **Rundles, R. W.,** and **Falls, H. F.:** Am. J. Med. Sci., **211,** 641, 1946.

16. **Singer, K., Chernoff, A. I.,** and **Singer, L.:** Blood, **6,** 413, 1951.
17. **Strumia, M. M., Taylor, L., Sample, A. B., Colwell, L. S.,** and **Dugan, A.:** Blood, **10,** 429, 1955.
18. **Sturgis, C. C.:** Hematology, 2nd ed. Springfield, Illinois: Charles C Thomas, p. 1222, 1955.
19. **Trinick, R. H.:** Lancet, **1,** 963, 1948.
20. **Vischer, A.:** Ztschr. f. klin. Med., **135,** 133, 1938.
21. **Weinstein, I. M., Spurling, C. L., Klein, H.,** and **Necheles, T. F.:** Blood, **9,** 1155, 1954.
22. **Wilson, H. E.,** and **Long, M. J.:** Am. J. Med., **14,** 534, 1953.
23. **Wyandt, H., Bancroft, P. M.,** and **Winship, T. O.:** A.M.A. Arch. Int. Med., **68,** 1043, 1941.

SUMMARIO IN INTERLINGUA

Elliptocytosis: Un Studio de Superviventia Erythrocytic per Medio de Chromium Radioactive (Cr^{51})

Es presentate un caso de elliptocytosis associate con non-compensate anemia hemolytic. Esseva constatate per medio del methodo a chromato (Cr^{51}) de natrium que le auto-superviventia erythrocytic esseva reducite. Le medie vita esseva 18,5 dies. Le litteratura relative al superviventia erythrocytic in elliptocytosis esseva revidite. Le presente caso es le prime unquam reportate con un demonstratemente reducite tempore de autosuperviventia.

VENTILATORY AND LUNG VOLUME DETERMINATIONS IN PATIENTS WITH CHEST DEFORMITIES*

By Harry N. Iticovici, M.D.
RESEARCH FELLOW

AND

Harold A. Lyons, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

(From The Cardiopulmonary Laboratory, State University of New York College of Medicine at New York City, and the Kings County Hospital, Brooklyn, New York)

Physiologic studies are rarely reported on patients with chest deformities and free of symptoms of a pulmonary or cardiac nature. This is a study of the ventilatory and lung volume measurements in 7 patients with thoracic deformities of different types. It is not a complete study, but one to indicate the patterns of physiologic ventilatory and volume changes to be expected in this type of patient.

Seven patients with chest deformities were studied: 2 patients with kyphoscoliosis, 2 patients with Marie-Strümpell disease, 2 patients with pectus excavatum, and one patient with fusion of the spine for correction of an idiopathic scoliosis.

Methods. All of these patients were admitted to the hospital or outpatient department for reasons other than cardiorespiratory complaints. Tidal volume, vital capacity, expiratory reserve, and inspiratory capacity were measured with a standard Collins respirometer having low resistance valves. The actual vital capacity and timed vital capacity were determined with the Collins vitalometer. The maximum breathing capacity measurement was made by collection of expired volume in a Douglas bag and the use of a Hans-Rudolph valve (Comroe[4]). Predicted values for total lung volume, vital capacity and maximum breathing capacity were calculated by the Cournand regression formulas (Baldwin, Cournand and Richards[1] and Comroe[4]). The functional residual volume and the index of intrapulmonary mixing were measured by the open circuit method of Darling[4].

Clinical Summaries. CASE 1. J.B. is a colored girl, 15 years old. Her scoliosis was first noted in 1949. She was admitted to the University Division Service of Kings County Hospital in 1953 with the diagnosis of idiopathic scoliosis. The history gave no cardiac or respiratory symptoms; she had a bilateral spinal fusion from T_4 to L_1 in three stages during the years 1953 and 1954. The physical examination revealed diminished breath sounds over the right chest posteriorly. The examination of the heart was within normal limits. The pulmonary function studies were done 5 months after the last operation.

The roentgenogram of the chest showed scoliosis of the dorsal spine with convexity to the right and scoliosis of the lumbar spine with convexity to the left. The heart had a mitral configuration due to rotation produced by the chest deformity (Figs. 1 and 2).

CASE 2. C.H. is a 53-year-old colored man who was admitted to the University Division Medical Service of Kings County Hospital in January, 1954, because of swelling of the breast that was later diagnosed as gynecomastia. At the age of 6 he had had Pott's disease. At age 19 he had had an exacerbation of the disease with paraplegia. On bed rest there was a gradual return of function in both lower extremities. In 1947, he developed weakness in the right lower extremity. On admission, he walked with difficulty. He complained of dyspnea after climbing a flight of steps or walking half a block. Physical examination revealed marked kyphoscoliosis, weakness and atrophy of the muscles of the right thigh. The

*These studies were aided by a contract between the Office of Naval Research, Department of the Navy and State University of New York.

TABLE 1.—THE OBSERVED VALUES AND PREDICTED VALUES FOR THE
WITH THE DETERMINED MIXING

Patient	*Age*	*Sex*	*Height (cm.)*	*Weight (kg.)*	*B.S.A. m^2*	*Observed Vital Capacity (Liters)*	*Per Cent of Predicted*	*One Second Timed Vital Capacity*	*Maximum Breathing Capacity (Liters/min.)*	*Per Cent of Predicted*	*Inspiratory Capacity (Liters)*	*Predicted Inspiratory Capacity*
1. J.B.	16	F	172	56	1.65	2400	69	91	105	100	2215	2258
2. C.H.	53	M	142	49	1.37	900	29	75	70	87	889	2003
3. A.D.	33	M	150	35.9	1.24	1220	34	30	44	52	1158	2369
4. S.M.	65	M	156	60	1.59	1840	58	56	63.7	77	1910	2068
5. M.V.	24	F	157	49	1.47	1600	52	87	73	83	1493	1980
6. H.F.*	11½	M	148	37	1.20	2490	100	89	58	75	**	**
7. C.K.	39	M	175	60	1.73	3700	90	57	92	81	3655	2651

* The normal values are difficult to ascertain since there is wide variation in this age group as shown by previous studies.[5,6,10]
** No predicted values on children.

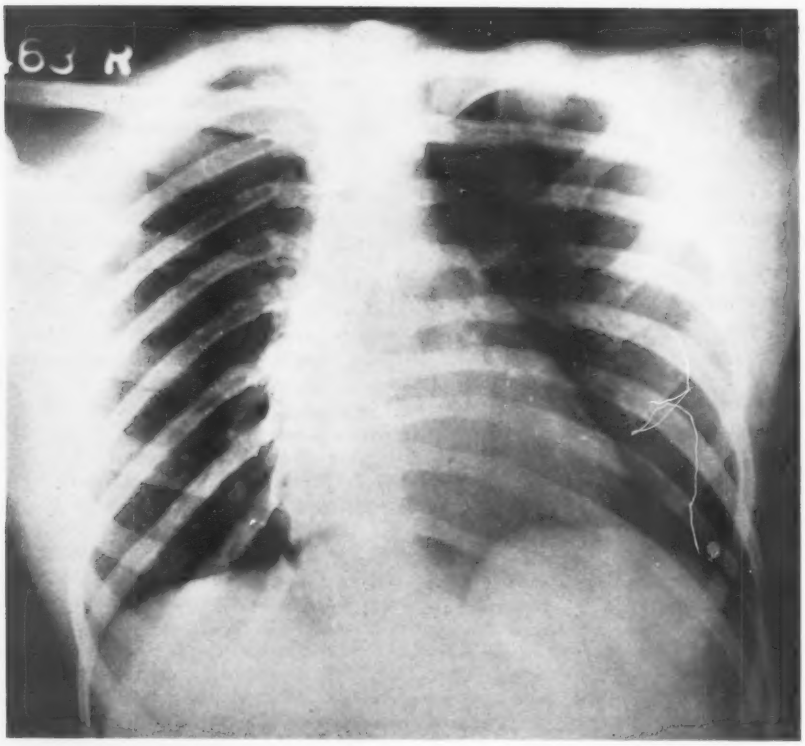


Fig. 1.—PA chest roentgenogram of patient J.B. One notes the scoliosis with convexity to the right.

VENTILATORY MEASUREMENTS AND LUNG VOLUME AND ITS SUBDIVISIONS
INDEX FOR THIS GROUP OF PATIENTS

Predicted Inspiratory Capacity	Per Cent of Predicted	Expiratory Reserve (Liters)	Predicted Expiratory Reserve	Per Cent of Predicted	Recumbent Vital Capacity	Predicted Vital Capacity	Per Cent of Predicted	Residual Volume (Liters)	Predicted Residual Volume	Per Cent of Predicted	Total Lung Capacity	Predicted Total Lung Capacity	Per Cent of Predicted
2258													
2003	98	620	1216	51	2835	20.2 × 172 = 3474	82	518	870	60	3353	4350	77
2369	44	133	1078	12.3	1022	21.7 × 142 = 3081	33	1040	1300	80	2064	4400	47
2068	49	178	1276	13.9	1336	24.3 × 150 = 3645	37	408	900	45	1744	4400	40
1980	92	180	1114	16.1	2090	20.4 × 156 = 3182	66	1160	1400	83	3250	4000	71
**	75	362	1066	34	1855	19.4 × 157 = 3046	61	1108	754	147	2963	3800	78
2651	**	**	**	**	2490	**	**	790	**	**	3435	**	**
	138	847	1427	59	4502	23.3 × 175 = 4078	110	475	1240	38	4950	5280	92

Fig. 2.—The AP roentgenogram of the spine of patient J. B. showing in greater detail the amount of the spinal deformity.

heart was displaced to the left. The hemoglobin was reported as 12 gm.

Posteroanterior-view roentgenograms of the chest (Figs. 3 and 4) show a decrease in the volume of the lungs. The posteroanterior film of the spine shows scoliosis with convexity to the left. Lateral film of the spine shows fusion and deformity of the vertebrae from T_5 to L_1 with resulting angulation in this area.

CASE 3. A.D. is a white man, 30 years old.

Fig. 3.—PA chest roentgenogram of patient C.H. which shows the decreased volume of the lung.

He was admitted to the University Division Medical Service of Kings County Hospital because of abdominal pain and diarrhea of 5 weeks' duration. He had had poliomyelitis at the age of 14 months and had had empyema of the right chest at the age of 5 years. This was drained surgically. He had no cardiac or pulmonary symptoms on admission. Physical examination revealed severe kyphoscoliosis. The trachea was deviated to the right. The lungs were clear to percussion and auscultation. There was marked muscular atrophy of all extremities. He could walk wearing a brace on the left lower extremity. In September, 1954, he had a resection of a segment of small bowel and ascending colon for regional enteritis. The postoperative course was uneventful. The hemoglobin was reported as 11.5 gm.

The posteroanterior roentgenogram of the chest showed scoliosis of the lumbar spine with convexity to the left. The lung volume is decreased. The lateral film of the chest showed a marked kyphosis.

CASE 4. S.M. is a white man, 65 years old, who has been seen in the outpatient department of the University Medical Service at Kings County Hospital since 1951. He has had arthritis since the age of 28. He complained of stiffness and pain in the back. Physical examination revealed that he walked stooped. His spine was rigid and he could

not extend his head. There was a moderate kyphosis of the spine. Examination of the heart and lungs was within normal limits. The hemoglobin was reported as 11.5 gm.

Posteroanterior film of the chest (Figs. 5 and 6) shows prominence of the aortic knob and a tortuous aorta, compatible with the age of the patient. No parenchymal infiltrate

onset of the disease was 5 years ago. For the past 2 years she has had limitation of motion and pain in the thoracic and lumbar spine. Physical examination revealed limitation of motion of the neck and back. The patient walked in a stooped position. The examination of the heart and lungs was within normal limits. The hemoglobin was reported as 9

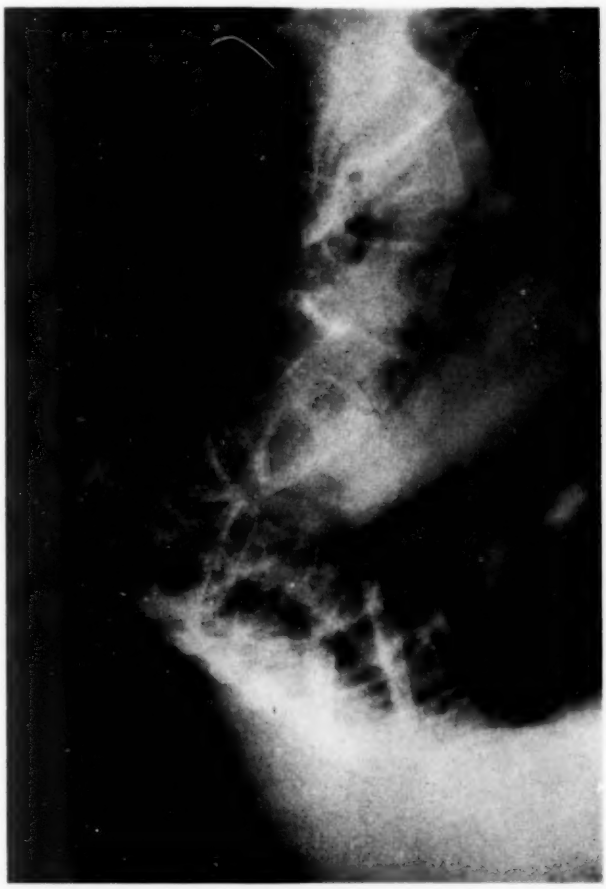


Fig. 4.—A lateral roentgenogram of the spine showing the marked kyphoscoliotic deformity.

is seen. The anteroposterior film of the spine shows a typical bamboo spine with fusion of the vertebrae. The lateral film of the spine shows the anterior ligament of the spine to be calcified.

CASE 5: M.V. is a white woman, 24 years old, who was admitted from the outpatient department in June, 1954, with the diagnosis of rheumatoid arthritis and spondylitis. The

gm. Roentgenogram of the chest showed normal pulmonary fields. Roentgenogram of the thoracic and lumbar spine showed involvement of the sacroiliac synchondrosis and obliteration of the various apophyseal articulations of the lumbar and dorsal spine.

CASE 6. H.F. is a white boy, 11½ years old. He was admitted to the hospital because of unexplained thrashing about in bed. One year

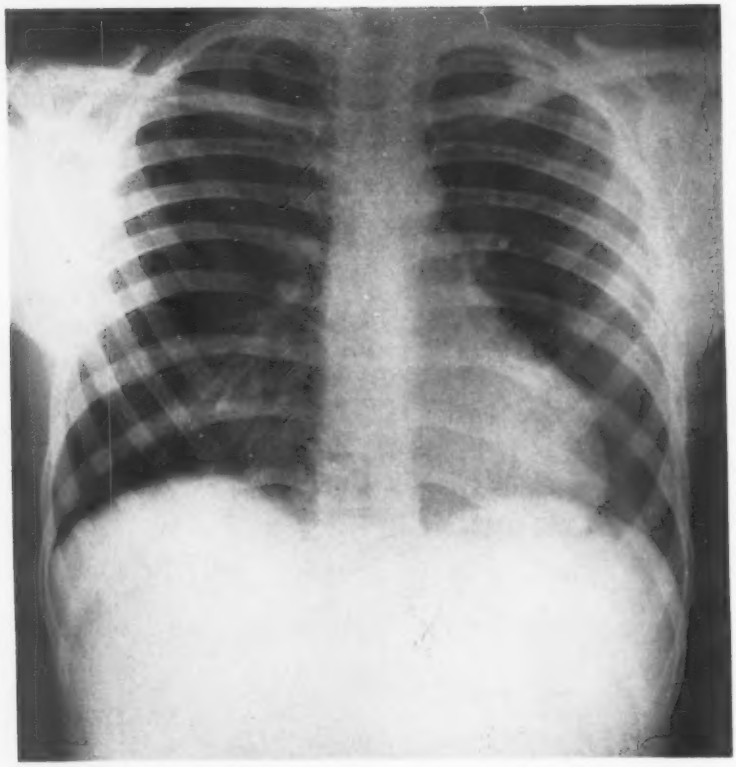


Fig. 5.—PA chest roentgenogram of patient S.M.

Fig. 6.—AP roentgenogram of the spine of patient S.M. showing the typical bamboo type of spinal deformity.

previous to admission he had had a grand mal seizure. The patient had no cardiorespiratory symptoms. He had funnel chest since infancy. He could stand the same amount of exercise as the other boys at school. Physical examination revealed a pectus excavatum. The deformity involved the lower end of the sternum and was 3 cm. deep and 6 cm. wide. The lungs were clear to percussion and auscultation. The heart was displaced to the left. The hemoglobin was reported as 13.5 gm.

The posteroanterior view of the chest (Fig. 7) reveals no parenchymal lesion. Lateral film of the chest (Fig. 8) shows the deformity of the sternum.

CASE 7. C.K. is a white man, 39 years old, who was admitted to the hospital because of diabetic gangrene of the left foot. He has been a known diabetic for the last 15 years. He has had pectus excavatum since early infancy. The examination of the lungs was otherwise normal. While he was in the hospital, he had a left lumbar sympathectomy and the amputation of two toes, with an uneventful recovery. The hemoglobin was reported as 11 gm., while the posteroanterior roentgenogram of the chest showed no parenchymal lesion. The heart was in midline. The lateral film of the chest showed the deformity of the sternum similar to that seen in patient H.F.

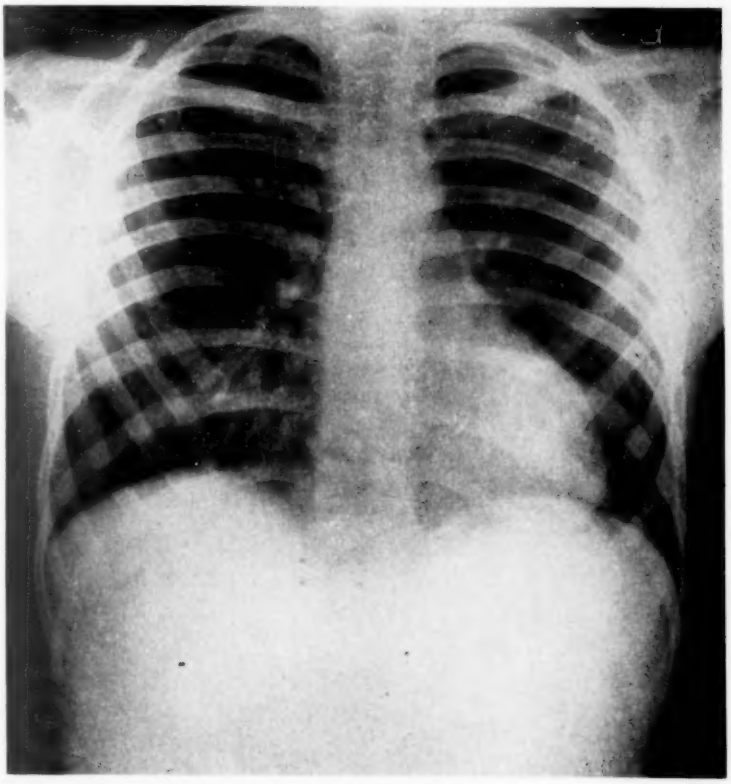


Fig. 7.—PA view of the chest of patient H.F. showing normal pulmonary fields and displacement of cardiac shadow to the left.

Discussion. An examination of the observed values for the maximum breathing capacity and vital capacity of all 7 patients shows the reduction of these values. Figure 9 is a graph on which the percentage of predicted values for vital capacity and maximum

breathing capacity are charted. In the patients with kyphoscoliosis and Marie-Strümpell disease, both the vital capacity and the maximum breathing capacity are reduced. In comparison with the normal predicted values (NL) because the residual volume is near the normal values. This phenomenon is probably due to the limitation of chest expansion caused by these conditions (Hart *et al.*[9] and Zudhi and Lyons[14]). A high ratio of residual vol-

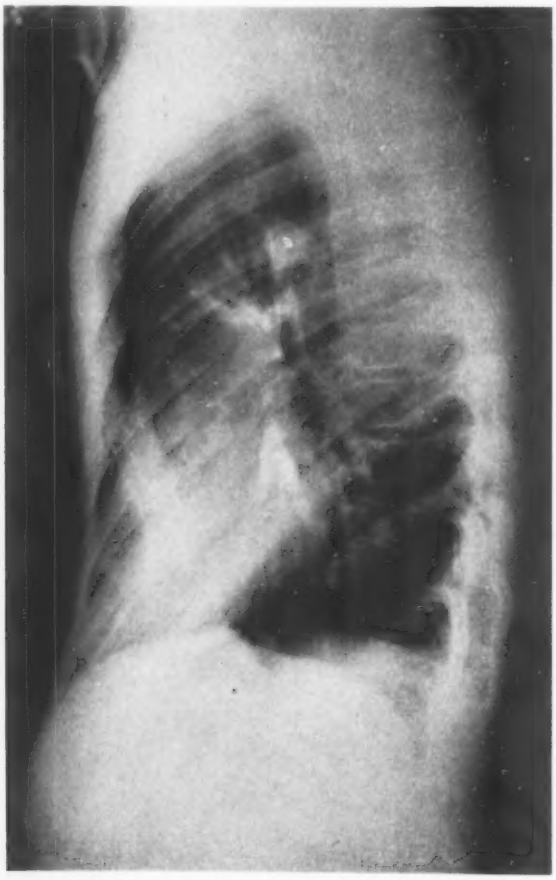


Fig. 8.—Lateral roentgenographic view of the chest of patient H.F. showing the deformity and depression of the sternum.

the most striking effect is the reductions in these values of the vital capacity and the total lung capacity. With this finding there is an increase in the ratio of residual volume to total lung capacity. The explanation for this must be the reduction of the vital capacity, ume to total lung capacity is misleading in being considered as a finding of emphysema. Wright[13] has cautioned against this interpretation without a consideration of absolute values. In emphysema, the total lung capacity may be normal or increased and the

residual volume increased, but in this group of patients the residual volume is fairly normal but the total lung capacity is reduced. It is this latter measurement which is responsible for producing the increased ratio. The normal intrapulmonary mixing values, the lack of dyspnea and only a moderate

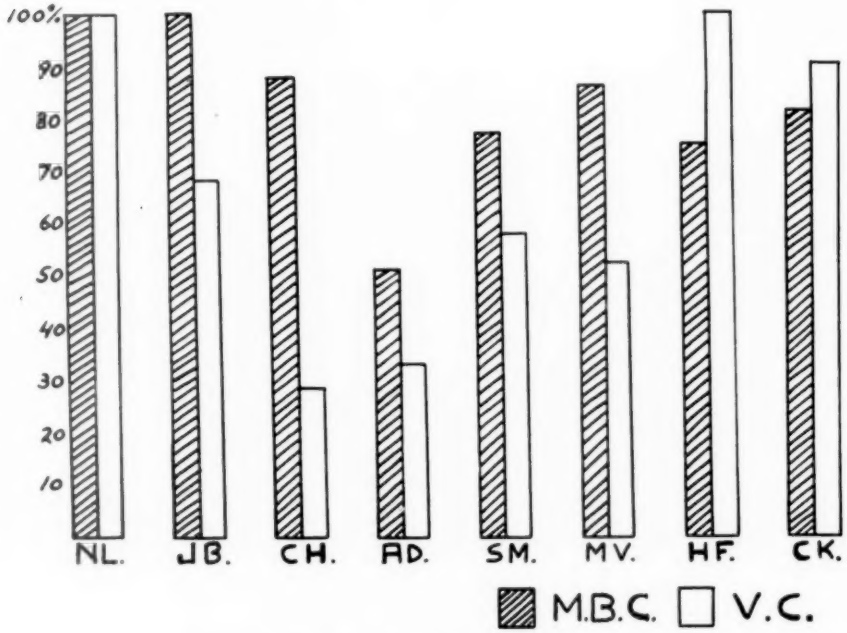


Fig. 9.—Graph of the observed maximum breathing capacity and vital capacity as percentages of the predicted values for the patients studied. NL. represents the normal predicted percentage values.

reduction in the maximum breathing capacity argue against the presence of emphysema. Because the vital capacity reduction is the most significant finding, and proportionately much greater than the reduction of the maximum breathing capacity, a restrictive type of ventilatory pattern is present.

The less significant reduction of the maximum breathing capacity in these patients also suggests that they could achieve a rate of at least 40 per minute (Ogilvie, Stone and Marshall[11]) or were able to use an unusually large proportion of their vital capacity during this measurement. In the patients with Marie-Strümpell disease there is very free diaphragmatic movement which has been observed (Hart *et al.*[9] and Zudhi and Lyons[14]). That diaphragmatic action contributes to three-fourths of the vital capacity has been shown objectively by Wade[12].

The data of the other 2 patients with pectus excavatum show that the maximum breathing capacity is reduced with a normal vital capacity. According to Gaensler's criteria[8], these would be classified as an obstructive type of breathing pattern, and might indicate associated emphysema. However, the timed vital capacity measurements are

within normal limits in the younger patient, reduced in the older, and both have normal residual volume to total lung capacity ratios and both have normal intrapulmonary mixing measurements. These findings would rule out the presence of emphysema, and the maximum breathing capacity abnormality can be explained on the basis of the inability to move air rapidly due to the chest deformity. Also, in both of these patients, the performance of the maximum breathing capacity test produced chest pain, which may also be a factor in curtailing the degree of maximum ventilation. In essence, the ventilatory disturbances in these patients are of the restrictive type.

A comparison of the absolute total lung capacities is shown in Fig. 10. These data in the group of kyphoscolitic patients relate well with the small lung volumes visualized on radiographic examination and the necropsy reports of lungs weighing 100 to 300 gm. less than normal, even when these lungs were edematous. The inspiratory capacity, expiratory reserve, and residual volumes are also shown. The patients with kyphoscoliosis and Marie-Strümpell disease show all of these subdivisions to be reduced. In the 2 patients, C.H. and A.D., with the greatest reduced values, the expiratory reserve is markedly reduced. It is believed that with progress of the disease, this portion of the lung volume may almost disappear. This low expiratory reserve with the near normal residual volume produces a small functional residual

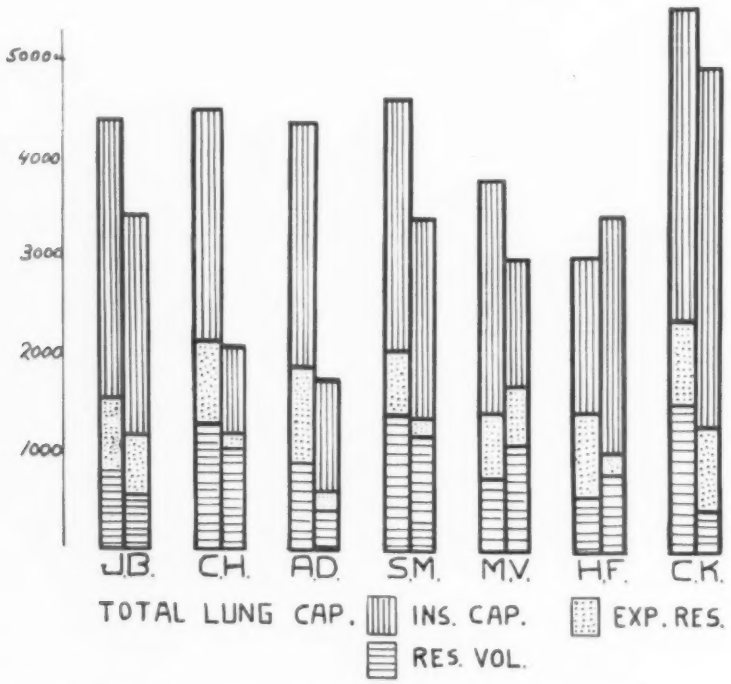


Fig. 10.—Graph showing the relation of the observed total lung capacity and its subdivisions as compared to predicted values for the patients studied.

capacity which may account for the exceptionally low intrapulmonary mixing indices found (Birath[2]).

Summary. An examination of the observed values for the maximum breathing capacity and vital capacity of 7 patients with thoracic deformities shows the reduction of these values. In the patients with kyphoscoliosis and Marie-Strümpell disease, both the vital capacity and the maximum breathing capacity are reduced. In comparison with normal predicted values, the most striking effect is the reductions in these values of the vital capacity and the total lung capacity. With this finding there is an increase in the ratio of residual volume to total lung capacity. The explanation for this must be the reduction of the vital capacity, because the residual volume is near the normal values. This phenomenon is probably due to the limitation of chest expansion caused by these conditions.

Data achieved by other means in a group of kyphoscolitic patients relates well with the small lung volumes visualized on radiographic examination and by necropsy. Patients with kyphoscoliosis and Marie-Strümpell disease show a reduction in the inspiratory capacity, expiratory reserve, and residual volumes. In 2 patients who showed the greatest reduced values, the expiratory reserve is also markedly reduced. It is believed that with progress of the disease, this portion of the lung volume may almost disappear. This low expiratory reserve with the near normal residual volume produces a small functional residual capacity which may account for the exceptionally low intrapulmonary mixing indices found.

The abnormalities found are characterized by a decreased total lung volume due to decreased expansibility of the chest wall with an accompanying restrictive breathing pattern.

REFERENCES

1. **Baldwin, E. deF., Cournand, A.,** and **Richards, D. W., Jr.:** Medicine, **27,** 243, 1948.
2. **Birath, G.:** Acta med. scandinav., Suppl. No. 154, 1, 1945.
3. **Chapman, E. M., Dill, D. B.,** and **Graybiel, A.:** Medicine, **18,** 167, 1939.
4. **Comroe, J. H.** (Ed.): Methods in Medical Research, Vol. 2. Chicago: Year Book Publishers, Inc., 1950.
5. **Ferris, B. G., Jr., Whittenberger, J. L.,** and **Gallagher, J. R.:** Pediatrics, **9,** 659, 1952.
6. **Ferris, B. G., Jr.,** and **Smith, C. W.:** Ibid., **12,** 341, 1953.
7. **Fisher, J. F.,** and **Dolehide, R. A.:** A.M.A. Arch. Int. Med., **93,** 687, 1954.
8. **Gaensler, E. A.:** Am. Rev. Tuberc., **64,** 256, 1951.
9. **Hart, F. O., Robinson, K. C., Allchin, F. M.,** and **Maclagan, N. F.:** Quart. J. Med., **18,** 217, 1949.
10. **Morse, M., Schultz, F. W.,** and **Cassels, D. E.:** J. Clin. Invest., **31,** 380, 1952.
11. **Ogilvie, C. M., Stone, R. W.,** and **Marshall, R.:** Clin. Sci., **14,** 101, 1955.
12. **Wade, O. L.:** J. Physiol., **124,** 193, 1954.
13. **Wright, G. W.:** Discussion of paper by **Gaensler, E. A.,** and **Strieder, J. W.,** J. Thor. Surg., **22,** 59, 1951.
14. **Zudhi, M. N.,** and **Lyons, H. A.:** Unpublished observations.

(Interlingua on page 328)

FIBRINOGEN CONCENTRATION IN VARIOUS CLINICAL CONDITIONS

By Samuel Losner, M.D.

and

Bruno W. Volk, M.D.

(From the Isaac Albert Research Institute and the Departments of Laboratories and Medicine, Jewish Chronic Disease Hospital, Brooklyn, New York)

A rapid determination of fibrinogen developed in recent years by the authors[16] has been applied to the diagnosis and evaluation of a variety of clinical conditions such as acute myocardial infarction, rheumatic fever with and without carditis, diabetic and arteriosclerotic gangrene, as well as some forms of hepatic disease. This method, derived from the photoelectric modification of the one-stage Quick prothrombin time, offers the dual advantage of determining both prothrombin and fibrinogen simultaneously. The latter is easily calculated from the difference in optical densities before and after clotting of a plasma-thromboplastin mixture. It has been shown previously that the increase in transmittance of light at the time of clotting can be correlated with the fibrinogen concentration by means of an exponential function[21]. We have been able to establish a simple linear relationship between plasma fibrinogen and the increase in optical density[16]. This procedure was termed by us "clot density method."

Observations. A. ACUTE MYOCARDIAL INFARCTION. This study includes 75 patients (26 women and 49 men) whose ages ranged from 38 to 81 and who had sustained an acute coronary occlusion. Plasma fibrinogen was determined 3 times weekly. Electrocardiograms were taken at frequent intervals. In 29 patients whose illness in the initial phase appeared particularly grave, anticoagulant therapy was instituted.

The earliest elevation of the plasma fibrinogen above normal was encountered 24 hours after the acute onset. Within 48 hours all patients disclosed a significant elevation of fibrinogen which continued to increase during the first week and reached its peak within 4 or 5 days (Fig. 1). In uncomplicated cases, the fibrinogen level gradually declined during the subsequent 2 weeks to reach normal values during or at the end of the 3rd week. A secondary rise of the fibrinogen concentration was observed in patients who had recurrence of symptoms or thromboembolic phenomena. In gravely ill patients the maximum fibrinogen concentration during the first week of illness exceeded 800 mg. and at times was even above 1300 mg. per 100 ml. The mortality rate in this group was 37.9% (11 out of 29 patients). On the other hand, the corresponding value in patients whose maximum fibrinogen level was less than 800 mg. per 100 ml. was only 8.7 (4 out of 46 patients).

B. PULMONARY EDEMA DUE TO LEFT VENTRICULAR FAILURE. While occasional episodes of pulmonary edema due to left ventricular failure were observed among the 75 patients with acute myocardial infarction either at the onset of the disease or after the 3rd week, a separate group of 8 patients was observed with a recurrent form of pulmo-

nary edema. In either instance, the fibrinogen concentration was elevated, and rose higher with each recurrent paroxysm. Thus, the failure of the fibrinogen level to return to normal in patients with acute myocardial infarction during and after the 3rd week was interpreted as an ominous sign.

C. CORONARY INSUFFICIENCY. Twenty patients with angina pectoris were diagnosed as coronary insufficiency. In all of them electrocardiographic studies revealed either permanent abnormalities or transient T-wave changes.

In none of these patients did the fibrinogen concentration rise above normal. It usually remained at a plateau, although in some instances it displayed a slight elevation within normal range (Fig. 1).

D. RHEUMATIC FEVER IN VARIOUS STAGES OF ACTIVITY. Fifty-one patients with rheumatic fever, whose age ranged from 4 to 28 were followed serially with determinations of the plasma fibrinogen and C-reactive protein (CRP). According to their stage of rheumatic activity they were divided into 4 groups:

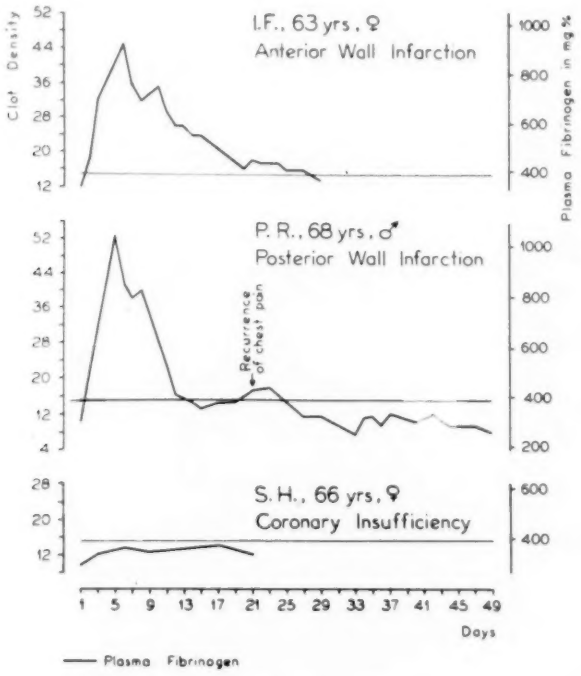


Fig. 1.—Course of the fibrinogen level in 2 cases of myocardial infarction and one case of coronary insufficiency.

1) Group I consisted of 30 patients with a monocyclic type of acute rheumatic fever. All but 4 of this group also had rheumatic carditis. 2) Group II included 3 patients with a polycyclic type of rheumatic fever and carditis. 3) Group III comprised 9 children recovering from a recent bout of acute rheumatic fever. 4) Group IV consisted of 9 patients with inactive heart disease.

All patients of Group I displayed significant fibrinogen elevations during the early stages of rheumatic activity. Its variations closely followed the clinical course. In 20 cases the increased fibrinogen level spontaneously declined to normal values before the institution of steroid therapy. In the remaining 10 patients it decreased to normal within 48 to 72 hours after administration of an adequate cortisone dosage. The fibrinogen level was characteristically depressed to subnormal levels during cortisone therapy (Fig. 2). Upon withdrawal of the hormone the fibrinogen level rose again whenever clinical manifestations of a "rebound" appeared. In mild cases of rheumatic fever the "rebound" was associated with a moderate fibrinogen rise. In severe cases, the "rebound" produced a marked fibrinogen elevation. The early decline of the fibrinogen level to normal following the "rebound" indicated that the patient was not undergoing a rheumatic exacerbation.

The clinical course of 3 patients in Group II correlated well with the fibrinogen level as did the electrocardiographic changes. Intercurrent infections of the respiratory tract were associated with a low-grade transient rise of the fibrinogen level whereas during rheumatic exacerbation it was markedly and consistently elevated. Its early return to normal presaged clinical amelioration.

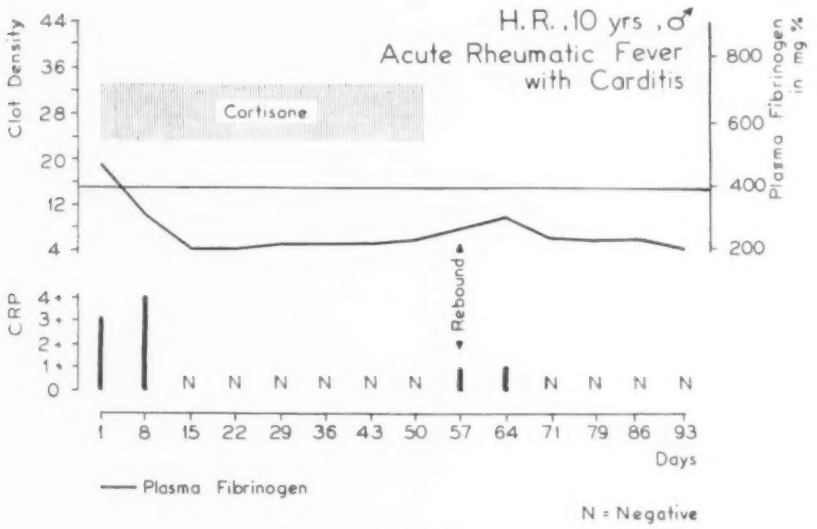


Fig. 2.—Early return of fibrinogen to normal upon institution of cortisone in a patient with acute rheumatic fever and carditis.

Similarly, patients of Group III with subsiding rheumatic fever failed to disclose any undue elevation of the fibrinogen level.

The 9 patients of Group IV with known rheumatic valvular heart disease who were studied for possible signs of activity also failed to disclose any significant rise of the fibrinogen level above normal. This finding confirmed the clinical diagnosis of intercurrent infection.

In 353 simultaneous determinations of fibrinogen and CRP of patients with rheumatic fever, a semi-quantitative

correlation was established between both values. In most instances the CRP was negative in the presence of normal fibrinogen values and positive whenever plasma fibrinogen was increased. Exceptions were, however, encountered in patients with upper respiratory infections or subsiding rheumatic fever. In the former, the CRP was positive while the plasma fibrinogen remained normal. In the other group, subsiding rheumatic activity was reflected by decreasing CRP and fibrinogen levels.

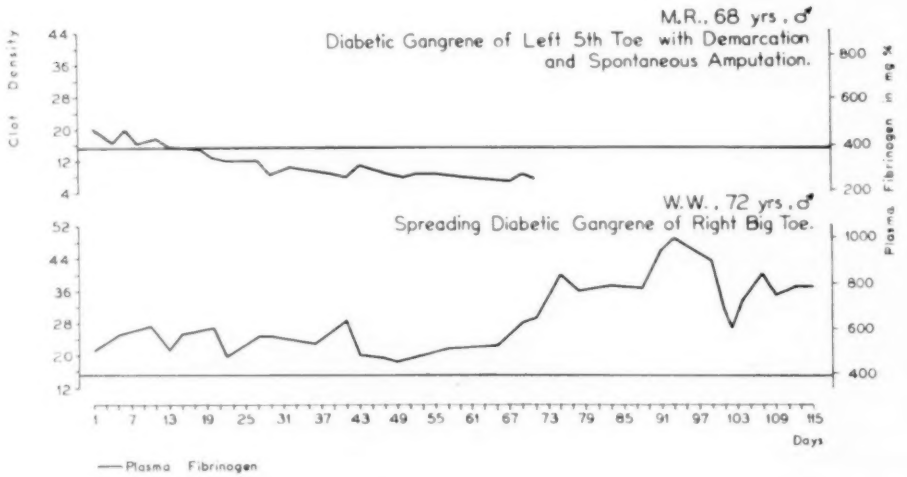

M.R., 68 yrs., ♂
Diabetic Gangrene of Left 5th Toe with Demarcation and Spontaneous Amputation.
W.W., 72 yrs., ♂
Spreading Diabetic Gangrene of Right Big Toe.
Clot Density
Plasma Fibrinogen mg %
Days
Plasma Fibrinogen

Fig. 3.—Normalization of fibrinogen levels in a patient with diabetic gangrene and demarcation in contrast to high and terminally increasing fibrinogen values in another patient with spreading diabetic gangrene.

One of the two proteins had a tendency, however, to normalize before the other, thus leading to transient dissociations.

E. BACTEREMIA. A pronounced dissociation between the values of CRP and fibrinogen was observed in 5 patients, 3 of whom had rheumatic valvular heart disease with subacute bacterial endocarditis caused by nonhemolytic streptococci. The 2 others had congenital heart disease and bacteremia due to *Staphylococcus aureus*. One of them also had roentgenologic evidence of pneumonia. In all instances the fibrinogen values were significantly normal despite a stormy course, whereas the CRP was positive.

F. DIABETIC AND ARTERIOSCLEROTIC GANGRENE. Plasma fibrinogen was studied serially in 8 patients with diabetic and in 2 with arteriosclerotic gangrene. Three of the patients with diabetic gangrene failed to improve and ultimately died. Their lesions were associated with considerable elevations of the fibrinogen level throughout the period of observation (Fig. 3). The remaining 7 patients whose lesions were demarcated and subsequently healed, displayed an early return of the initially elevated fibrinogen level to normal (Fig. 3). The normalization of the fibrinogen values occurred from 3 to 18 months before spontaneous amputation of the affected phalanx took place.

G. HEPATIC DISEASE. Prothrombin times and plasma fibrinogen levels were studied in 5 patients with obstructive jaundice, in 3 with infectious hepatitis

and in 2 with Laennec's cirrhosis. Patients with viral hepatitis displayed prolonged prothrombin times and low normal or subnormal fibrinogen levels from the very onset of the disease as did the 2 patients with Laennec's cirrhosis. On the other hand, the corresponding values in 5 patients with obstructive jaundice were normal. At times, the fibrinogen level was considerably elevated when the clinical picture suggested superimposed cholangitis. In all patients of this group the diagnosis was corroborated by a battery of other liver function tests.

Discussion. Among the various procedures available to determine the fibrinogen concentration, precipitation methods[4], determination of sedimentation constant by means of the ultracentrifuge[2], as well as electrophoretic[8], refractorimetric[28], gravimetric[29], turbidimetric[20], colorimetric[25] and Kjeldahl[5] methods have been utilized throughout the years. Aside from the technical difficulties which some of these methods entail, they frequently fail to separate fibrinogen from other proteins leading to an overlapping of the various fractions[3]. Similarly, electrophoretic analysis has revealed that small amounts of beta and gamma globulins are carried along together with fibrinogen[2]. The method which we have elaborated[16] is a thrombinogenic procedure. As such it is very likely that it determines fibrinogen only, since it is defined as the plasma protein which forms fibrin under the action of thrombin[19]. Moreover, since the entire procedure can be completed within 5 minutes, it is believed that the speed of the method eliminates the factor of protein degradation, thus enhancing its accuracy. The normal values of the "clot density" range from 5 to 15, corresponding to fibrinogen levels varying from 210 to 390 mg. per 100 ml.

Recently, the changes of a number of blood constituents in acute myocardial infarction have been the subject of clinical and laboratory studies. Some of them are enzymes widely distributed throughout the human body, such as SGO-transaminase[1,11,12] and serum aldolase, as recently reported by the authors[32]. Their concentration in serum rises whenever cellular disintegration occurs as in myocardial infarction due to the release of enzymes by necrotic tissue[1,11,12,32]. While it seems that an increase of these enzymes in serum is the immediate result of myocardial injury, subsequent changes in globulins[13], CRP[10], mucoproteins[11], fibrinogen[7,15,18] and erythrocyte sedimentation rate (ESR)[24] probably represent the phase of repair and healing. This distinction between the two groups of blood constituents may account for their different duration. Enzymes released after the acute injury lead only to a short-lasting elevation in serum not exceeding 4 or 5 days, whereas the various proteins remain elevated for 2 weeks or more. From a clinical viewpoint it seems that neither one nor the other group alone can adequately reflect the myocardial injury. The underlying pathologic process certainly extends over a longer period than that during which these enzymes are released into the blood stream. It is, therefore, believed that a battery of tests determining enzymes as well as fibrinogen levels may supplement the electrocardiographic findings so as ultimately to provide a better profile of the clinico-pathological entity of acute myocardial infarction. The ESR although still widely used in the evaluation of this condition in our experience has failed to indicate the severity of an acute myocardial infarction and particularly so in massive infarction with hemoconcentration[30]. On the other hand, the maximum fibrinogen concentration reflects the clinical events rather accurately. The explana-

tion advanced by us on clinical grounds mainly, that the fibrinogen level may indicate the extent of the infarcted area, has been confirmed in experimental studies in dogs[31]. A semiquantitative relationship has thus been demonstrated between the area of necrosis and the peak of the fibrinogen concentration.

In coronary insufficiency, the persistently normal fibrinogen level has been of great diagnostic help in contrast to the ESR and CRP which both may be abnormal in this condition[10].

Whereas the decline of the fibrinogen concentration during the 3rd week of acute myocardial infarction has been taken to indicate a favorable prognosis, its failure to return to normal values has been found to be associated with recurrent thrombosis or complications such as left ventricular failure or thromboembolic phenomena. Whenever pulmonary edema occurred, it caused a further increase of the fibrinogen level.

The dual advantage of simultaneous determination of prothrombin time and fibrinogen by the "clot density" method was of particular help in carrying out anticoagulant therapy with hypoprothrombinemic agents such as Dicumarol, Hedulin or Tromexan. None of these anticoagulants affect the fibrinogen concentration although they profoundly interfere with prothrombin production.

In acute rheumatic fever, the fibrinogen level, although generally lower than in acute myocardial infarction, is considerably elevated in accordance with the acuity of the rheumatic process[17]. A relatively benign monocyclic course is indicated either by a spontaneous decline of the fibrinogen level before instituting steroid therapy or else by an early normalization of the fibrinogen at a low level after the administration of cortisone. The subnormal fibrinogen concentration of patients under steroid therapy has been attributed to a nonspecific effect[6] upon fibrinogen production. We have been unable to demonstrate this phenomenon in normal children[9].

At the termination of a "rebound" fibrinogen is the first plasma protein to decline to normal level, thus presaging further clinical improvement. Although the CRP and fibrinogen have their place at different points in the plasma protein spectrum, a considerable degree of parallelism of both has been observed in acute rheumatic fever. During subsiding rheumatic fever the fibrinogen level may return to normal a day or two before the CRP.

In upper respiratory infections sustained by patients with rheumatic heart disease the CRP is usually positive despite absence of rheumatic activity while the fibrinogen level remains normal. The observation of a normal fibrinogen level and a markedly positive CRP in a group of 5 patients with acute and subacute bacterial endocarditis leads to the conclusion that bacteremia alone is not sufficient to increase fibrinogen production. This phenomenon is of particular interest in the presence of fever and the septic course of a disease. Cellular disintegration due to inflammatory or necrotizing lesions seems to be the only distinct cause of hyperfibrinogenemia.

An early decline of the fibrinogen level in patients with diabetic and arteriosclerotic gangrene seems to indicate demarcation of the lesions. In contrast, rising fibrinogen concentrations are associated with spreading gangrene ultimately ending fatally with septicemia, renal failure and terminal bronchopneumonia.

In 1935, Quick and associates demonstrated that the prothrombin time is prolonged in the plasma of various types of jaundice[23]. Experimentally, it was shown later that hepatotoxins produce a prothrombin deficiency as de-

termined by the two-stage prothrombin method[27]. Further studies on the differential diagnosis of various types of liver disease by Owren[22] revealed that factor V is normal or elevated in obstructive jaundice. In contrast, acute hepatitis is associated with a considerably lowered concentration of factor V. Similarly, his data seem to indicate that while the prothrombin level was always reduced in parenchymatous jaundice, it was mostly normal in the early phase of obstructive jaundice only to decline subsequently.

In our experience the prothrombin time is normal in the early stages of obstructive jaundice while it is prolonged in parenchymatous jaundice. Moreover, the simultaneous determination of the fibrinogen level revealed that the association of a low fibrinogen with prolonged prothrombin time is strongly suggestive of viral hepatitis. This seems to be particularly significant because both prothrombin and fibrinogen are formed in the liver[27]. In early obstructive jaundice, on the other hand, the association of a normal prothrombin time with a normal or elevated fibrinogen level can be of differential diagnostic significance. The fibrinogen values tend to increase considerably with supervening cholangitis.

Summary. 1) The fibrinogen level as determined by the rapid "clot density" method was studied serially in patients with acute myocardial infarction, coronary insufficiency, rheumatic fever in various stages of activity, acute and subacute bacterial endocarditis, diabetic and arteriosclerotic gangrene as well as in cases with hepatic disease.

2) In acute myocardial infarction the maximum fibrinogen level indicates the extent of the myocardial damage and the severity of a clinical condition.

3) Coronary insufficiency can be readily differentiated from myocardial infarction by the fibrinogen level which remains normal throughout.

4) In rheumatic fever the acuity of the disease correlates well with the fibrinogen level.

5) The fibrinogen level remains normal in bacteremia due to acute or subacute bacterial endocarditis while the CRP is markedly positive.

6) Demarcation of a gangrenous lesion is presaged by an early decline of the fibrinogen to normal.

7) Parenchymatous jaundice is associated with subnormal fibrinogen values whereas obstructive jaundice usually reveals high normal or distinctly elevated fibrinogen levels.

8) The serial determination of fibrinogen has proven to be a useful tool in the diagnosis, prognosis, and management of the above conditions.

REFERENCES

1. **Agress, C. M., Jacobs, H. I., Glassner, H. F., Lederer, M. A., Clark, W. G., Wroblewski, F., Karmen, A.,** and **LaDue, J. S.:** Circulation, **11**, 711, 1955.
2. **Armstrong, S. H., Budka, M. J. E.,** and **Morrison, K. C.:** J. Am. Chem. Soc., **69**, 416, 1947.
3. **Avery, A.,** and **Munro, F. L.:** Arch. Biochem., **16**, 33, 1948.
4. **Butler, A. M.,** and **Montgomery, H.:** J. Biol. Chem., **99**, 173, 1933.
5. **Cullen, G. E.,** and **Van Slyke, D. D.:** Ibid., **41**, 587, 1920.
6. **Farnley, G. R.,** and **Bunim, J. J.:** Lancet, **2**, 1113, 1951.
7. **Gilchrist, E.,** and **Tulloch, J. A.:** Edinburgh Med. J., **59**, 561, 1952.
8. **Hollander, F.:** Klin. Wchnschr., **19**, 436, 1940.
9. **Kanof, A., Losner, S.,** and **Volk, B. W.:** Pediatrics, **12**, 565, 1953.
10. **Kroop, I. G.,** and **Shackman, N. H.:** Proc. Soc. Exper. Biol. & Med., **86**, 95, 1954.
11. **LaDue, J. S., Wroblewski, F.,** and **Karmen, A.:** Science, **120**, 497, 1954.

12. **LaDue, J. S.,** and **Wroblewski, F.:** Circulation, **11,** 871, 1955.
13. **Linko, E.,** and **Waris, E.:** Scandin. J. Clin. and Lab. Invest., **7,** 135, 1955.
14. Iidem: Ibid., **7,** 141, 1955.
15. **Losner, S., Volk, B. W.,** and **Wilensky, N. D.:** A.M.A. Arch. Int. Med., **93,** 231, 1954.
16. **Losner, S., Volk, B. W., Jacobi, M.,** and **Newhouse, S.:** J. Lab. & Clin. Med., **38,** 28, 1951.
17. **Losner, S., Volk, B. W.,** and **Kanof, A.:** Am. Heart J., **50,** 100, 1955.
18. **Meyers, L.:** A.M.A. Arch. Int. Med., **82,** 412, 1948.
19. **Morrison, P. R.:** J. Am. Chem. Soc., **69,** 2, 1949.
20. **Nanninga, L.:** Arch. Neerl. De Physiol., **28,** 241, 1946.
21. **Nygaard, K. K.:** Hemorrhagic Diseases. Photelectric Study of Blood Coagulability. St. Louis: C. V. Mosby Company, 1941.
22. **Owren, P. A.:** Scandin. J. Clin. & Lab. Invest., **1,** 131, 1949.
23. **Quick, A. J., Stanley-Brown, M.,** and **Bancroft, F. W.:** Am. J. Med. Sci., **190,** 501, 1935.
24. **Rabinowitz, M. A., Shookhoff, C.,** and **Douglas, A. H.:** Am. Heart J., **7,** 52, 1931.
25. **Saifer, A.,** and **Newhouse, A.:** J. Biol. Chem., **208,** 159, 1954.
26. **Schulz, F. H.:** Das Fibrinogen. Leipzig: Georg Thieme, p. 124, 1953.
27. **Smith, H. P., Warner, E. D.,** and **Brinkhous, K. N.:** J. Exper. Med., **66,** 801, 1937.
28. **Starlinger, W.:** Biochem. Zentralbl., **140,** 203, 1923.
29. Idem: Ibid., **143,** 179, 1923.
30. **Volk, B. W.,** and **Losner, S.:** Am. Heart J., **47,** 658, 1954.
31. **Volk, B. W., Losner, S., and Crastnopol, P.:** Proc. Soc. Exper. Biol. & Med., **89,** 277, 1955.
32. **Volk, B. W., Losner, S., Aronson, S. M.,** and **Lew, H.:** Am. J. Med. Sci., **232,** 38, 1956.

SUMMARIO IN INTERLINGUA

Concentration de Fibrinogeno in Varie Conditiones Clinic

1. Le rapide methodo a "densitate de coagulo" esseva usate in le studio serial del nivello de fibrinogeno in patientes con acute infarcimento myocardial, insufficientia coronari, febre rheumatic in varie stadios de activitate, acute e subacute endocarditis bacterial, gangrena diabetic e arteriosclerotic, como etiam in casos de morbo hepatic.

2. In acute infarcimento myocardial le nivello maximal de fibrinogeno indica le grado del lesion myocardial e le severitate del condition clinic.

3. Insufficientia coronari es promptemente differentiabile ab infarcimento myocardial per le nivello de fibrinogeno que remane normal durante le integre curso de ille condition.

4. In febre rheumatic, le acuitate del morbo monstra un bon correlation con le nivello de fibrinogeno.

5. Le nivello de fibrinogeno remane normal in bacteremia debite a acute o subacute endocarditis bacterial, durante que le proteina reactive a C es marcatemente positive.

6. Le demarcation de un lesion gangrenose es precedite per reduction del nivello de fibrinogeno a valores normal.

7. Ictero parenchymatose es associate con subnormal valores pro fibrinogeno durante que ictero obstructive revela usualmente nivellos de fibrinogeno que es alte sed ancora normal o distinctemente elevate.

8. Le determination serial de fibrinogeno se ha provate utile in le diagnose, prognose, e manipulation del supra-listate conditiones.

THE NUMBER OF BLOOD CULTURES NECESSARY TO DIAGNOSE MOST CASES OF BACTERIAL ENDOCARDITIS

By James Belli, B.S., M.S.

AND

Burton A. Waisbren, M.S., M.D.
CLINICAL INSTRUCTOR OF MEDICINE

(From the Infectious Disease Control Unit of the Department of Medicine of the Milwaukee County General Hospital and the Marquette University School of Medicine, Milwaukee, Wisconsin)

The purpose of this investigation was to gain information regarding the number of blood cultures it is worth while to draw from patients suspected of having subacute bacterial endocarditis. It would be ideal if the causative organism could be identified in each case of endocarditis, but the problem often faced by the clinician is how long he should wait before beginning therapy. The long natural history of this disease makes it apparent that therapy need rarely be begun as an emergency (Osler[7]). However, the mortality rate of subacute bacterial endocarditis remains above 25%, and mycotic aneurysms, ruptured valves, septic emboli and intractable heart failure occur with increasing frequency as the disease progresses (Friedberg[3]). Furthermore, it has been well established that during certain phases of this disease the blood is consistently free of bacteria (Libman and Friedberg[5]). Therefore, if a prolonged search for a positive blood culture is pursued in each case of subacute bacterial endocarditis, not only will it be frequently futile, but, in certain cases, the resultant delay in therapy will be harmful to the patient.

In this report 82 bacteriologically proven cases of subacute bacterial endocarditis were studied to determine how many blood cultures it was necessary to draw before a positive result was obtained. This information should help one make a decision as to when to stop drawing cultures and to start therapy in cases in which bacterial endocarditis is the most likely diagnosis.

Material and Methods. The records of 82 cases of bacteriologically proven bacterial endocarditis who were seen at the Milwaukee County General Hospital between 1938 and 1954 were examined. The age and sex of the patient, the causative organism, prior therapy, the number of blood cultures necessary to make the diagnosis and the percentage of the total cultures that were positive were noted in each case. All blood samples were of venous blood and the usual procedure was to inject 5 ml. of blood into 20 ml. of tryptose phosphate* or beef infusion broth. Contaminated cultures were not included in the study.

Seventeen cases of subacute bacterial endocarditis in which the diagnosis was well established but in which repeated cultures were sterile were selected for comparison with the bacteriologically proven cases.

The 82 cases were divided into those due to *Streptococcus viridans* and those in which there were other causative organisms.

Results. Twenty of the 82 patients were female and 62 were male. Their ages ranged from 16 to 71 (Table 1). The causative organism was *Streptococcus viridans* in 35 cases, nonhemoly-

*Difco.

tic streptococci in 15, and *Micrococcus pyogenes* in 28. Other organisms were found in 4 cases. Three of the patients infected with *Streptococcus viridans* and 8 of those infected with other bacteria had received penicillin prior to the time that the first blood culture was drawn. The amount ranged from 30,000 to 8,600,000 units. These patients are designated as "treated" in the tables (Tables 3, 4 and 5).

TABLE 1.—AGE RANGE OF 82 PATIENTS WITH BACTERIOLOGICALLY PROVEN BACTERIAL ENDOCARDITIS

Age			
0–20	21–40	41–60	61–80
3	24	31	14

TABLE 2.—SPECIES OF BACTERIA THAT CAUSED THE 82 CASES OF BACTERIAL ENDOCARDITIS.

Causative Organism	*No. of Cases*
Streptococcus viridans	35
Nonhemolytic strep.	15
Micrococcus pyogenes	28
Diplococcus pneumoniæ	2
Hemophilus influenzæ	1
Gram-neg. bacilli (unidentified)	1

The numbers of blood cultures necessary to diagnose the 82 cases are shown in Table 3. It is important to note that 52 of the cases were diagnosed by the first culture and it was in only 6 cases that more than five were necessary. Of these six, five were due to organisms other than *Streptococcus viridans* and three had received previous treatment with penicillin.

The percentages of total cultures that were positive are shown in Table 4. It can be seen that, in the absence of previous therapy, over one-half of the cultures showed growth. Previous therapy, as might be expected, appeared to reduce the percentage of positive cultures (Tables 3 and 4). Endocarditis due to *Streptococcus viridans* was particularly apt to yield a positive culture within the first five samples (Table 5).

Table 6 compares the number of blood cultures drawn in 17 cases of "bacteria-free" endocarditis with the number necessary to make the diagnosis in the 82 culturally proven cases. Only 8% of the latter required more than four blood cultures for diagnosis,

TABLE 3.—THE NUMBER OF BLOOD CULTURES THAT WERE NECESSARY TO DIAGNOSE THE 82 CASES OF BACTERIAL ENDOCARDITIS

Etiologic Agent		*Number of Samples*								
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
		Number of cases in which sample was the first one positive								
Streptococcus viridans	Untreated	21	5*	2	3			1		
	Treated**	3								
Other organisms	Untreated	27	6	2	4	1	1			1
	Treated	1	1				1			2
Total		52	12	4	7	1	2	1		3

* For instance in 5 cases of previously untreated endocarditis due to *S. viridans* the first blood culture was negative and the second one was positive.

** Treated cases mean those in whom penicillin had been given before the blood cultures were drawn.

whereas 58% of the "bacteria-free" cases had more than four negative cultures. This comparison suggests that at least some of the so-called "bacteria free" cases fall into a group separate from the cases in which four blood cultures were sufficient for diagnosis.

The case in which 34 cultures were drawn had all the criteria for bacterial endocarditis and responded very well to therapy (Table 3). Since it was such a "classic" case, numerous cultures were taken at various times during the day to see if, by sheer persistence, a positive culture could be obtained. The failure to obtain growth in spite of fever, a high sedimentation rate, hematuria, a changing heart murmur, a pal-

TABLE 4.—THE PERCENTAGE OF CULTURES THAT WERE POSITIVE*

Etiologic Agent	*Type of Case*	*No. of Cases*	*Total Number of Cultures Drawn*	*Percentage of Positive Cultures in Untreated Cases*	*Percentage of Positive Cultures in Treated Cases*
Streptococcus viridans	Untreated	32	241	51%	...
Streptococcus viridans	Treated**	3	33		43%
Other organisms	Untreated	42	316	55%	
Other organisms	Treated	5	75		20%
Totals		82	665	53%	31.5%

* The average of cultures that were taken was 9.
** Treated cases mean those in whom penicillin has been given before the blood cultures were drawn.

TABLE 5.—THE NUMBER OF CASES IN THE VARIOUS GROUPS IN WHICH THE DIAGNOSIS WAS MADE WITHIN THE FIRST FIVE CULTURES

Streptococcus viridans				*Other Organisms*			
Diagnosis with First Five Samples		*Diagnosis with Second Five Samples*		*Diagnosis with First Five Samples*		*Diagnosis with Second Five Samples*	
Untreated	Treated*	Untreated	Treated	Untreated	Treated	Untreated	Treated
31	3	1	0	40	2	2	3

* Treated cases mean those in whom penicillin has been given before the blood cultures were drawn.

TABLE 6.—A COMPARISON BETWEEN THE NUMBER OF CULTURES NECESSARY TO MAKE THE DIAGNOSIS IN BACTERIOLOGICALLY PROVEN CASES OF ENDOCARDITIS AND THE NUMBER OF CULTURES DRAWN FROM THE "BACTERIA-FREE" CASES

	Number of Bacteriologically Proven Cases Diagnosed by Each Number of Cultures		*Number of "Bacteria-free" Cases in Whom Each Number of Cultures Had Been Drawn*	
No. of Cultures	*Number*	*% of the 86 Cases*	*Number*	*% of the 17 Cases*
1	52	60.5	0	0
2	14	16.3	1	5.9
3	4	4.7	2	11.75
4	9	10.5	2	11.75
5	1	1.1	6	35.3
6	2	2.3	0	0
7	1	1.1	1	5.9
8	0	0	0	0
9	3	3.5	0	0
10	0	0	2	11.75
11	0	0	2	11.75
34	0	0	1	5.9
Total	82	100.00	17	100.00

pable spleen and a subsequent response to therapy, certainly suggests that this patient was in the so-called "bacteria-free" phase of his disease[5].

Discussion. The results of this study are in essential agreement with those of other workers. Beeson, Brannon and Warren showed that organisms are discharged into the blood stream at a regular rate and this helps explain the high percentage of positive cultures in the bacteriologically proven cases[1]. They also noted a higher bacterial count in arterial blood than in venous blood[1]. Mallen, Hube and Brenes, on the other hand, found no advantage in arterial over venous cultures, but pointed out the advantages of bone marrow cultures for the diagnosis of bacterial endocarditis[6]. Both bone marrow and arterial cultures have been taken routinely on the medical service of the Milwaukee County General Hospital during the past 3 years and as yet we have failed to be impressed with results obtained from them.

Kelson and White reviewed the literature and found 71% of blood cultures positive in cases of bacteriologically proven bacterial endocarditis[4]. This is higher than the over-all percentage of 41% positive cultures found in this study. Libman and Friedberg also cited a higher figure and state that 85 to 90% of cultures are positive in proven cases[5]. The fact that some of our cases had previous therapy with antibiotics may explain the lower percentage in our series.

The method of investigation used did not take into consideration the additional number of cases of bacterial endocarditis that might have been diagnosed had more blood cultures been taken. There is little doubt that the number drawn in a hospital population will be directly related to the number of cases of bacterial endocarditis that are diagnosed, and this study in no way invalidates this truism. However, in the established cases in which no blood cultures were positive, it did not appear as if the failure to obtain a positive result was due entirely to the lack of a sufficient number being drawn. Thus the data do make it reasonable to begin therapy in a suspected case of bacterial endocarditis after a limited number of blood cultures have been drawn and support the concept of Libman of a definite abacterial phase in certain cases[5]. Because of this it has become our convention to draw five venous, one arterial, and one bone marrow culture in a suspected case of bacterial endocarditis. If these are negative and if the patient meets the criteria for this disease advanced by Friedberg[3] (an unexplained fever of 2 weeks' duration in a patient with valvular heart disease and normal sinus rhythm), we are of the opinion that it is justifiable to begin therapy with adequate doses of penicillin and streptomycin (Finland[2]). Our data should not be construed as discounting in any way the desirability of obtaining an etiologic agent in a particular case of bacterial endocarditis. It is suggested, however, that if five blood cultures are already negative there is a considerably decreased chance of obtaining a positive result, and this should be considered when the decision is made regarding the time to begin therapy for a particular patient.

Summary and Conclusions. In 77 of 82 cases of bacterial endocarditis, the first positive blood culture was obtained within the first five cultures. Fifty-two of the cases were diagnosed by the first that was drawn. In no cases were more than ten cultures necessary to make the diagnosis. Forty-one per cent of all cultures that were drawn were positive.

This study indicates that after five

sterile blood cultures there is a decreasing possibility of making a bacteriologically proven diagnosis of subacute bacterial endocarditis. Under these circumstances it is justifiable, therefore, to begin therapy in order to reduce valve damage and other complications of this disease.

REFERENCES

1. **Beeson, P. B., Brannon, E. S.,** and **Warren, J. V.:** J. Exper. Med., **81**, 9, 1945.
2. **Finland, M.:** Circulation, **9**, 292, 1954.
3. **Friedberg, C. K.:** J. Am. Med. Assn., **144**, 526, 1950.
4. **Kelson, S. R.,** and **White, P. D.:** Ann. Int. Med., **22**, 40, 1945.
5. **Libman, E.,** and **Friedberg, C. K.:** Oxford System of Medicine, **2**, 346, 1949.
6. **Mallen, M. S., Hube, E. L.,** and **Brenes, A.:** Am. Heart J., **33**, 692, 1947.
7. **Osler, W.:** Lancet, **1**, 415, 1885.

SUMMARIO E CONCLUSIONES IN INTERLINGUA

Le numero de Culturas Sanguinee Necessari pro le Diagnose del Majoritate del Casos de Endocarditis Bacterial

In 77 casos de un series de 82 casos de endocarditis bacterial, le prime positive cultura sanguinee esseva obtenite inter le prime cinque culturas. Cinquanta-duo casos esseva diagnosticate super le base del prime cultura obtenite. In nulle caso esseva necessari pro le diagnose plus que dece culturas. Quaranta-un pro cento de omne culturas obtenite esseva positive.

Iste studio indica que post cinque sterile culturas sanguinee le probabilitate decresce de un diagnose, bacteriologicamente verificate, de subacute endocarditis bacterial. Ergo in iste circumstantias il es justificabile comenciar le therapia a fin de reducer damnos al valvulas e le altere complicationes de iste morbo.

A THERAPEUTIC EVALUATION OF 1-ALLYL-3-ETHYL-6-AMINOTETRAHYDROPYRIMIDINEDIONE (MICTINE*) A NEW ORAL DIURETIC

By Leonard P. Caccamo, M.D.
ASSISTANT SECTION CHIEF, CARDIOLOGY, VETERANS ADMINISTRATION HOSPITAL
INSTRUCTOR IN INTERNAL MEDICINE, WAYNE UNIVERSITY SCHOOL OF MEDICINE

B. H. Pringle, Ph.D.
CHIEF, MEDICAL RESEARCH, VETERANS ADMINISTRATION HOSPITAL
INSTRUCTOR IN PHYSIOLOGICAL CHEMISTRY, WAYNE UNIVERSITY SCHOOL OF MEDICINE

AND

Dale E. Hissong, B.S.
BIOCHEMIST, RESEARCH DIVISION, VETERANS ADMINISTRATION HOSPITAL

(From the Cardiology Section, Veterans Administration Hospital, Dearborn, Michigan, and the Department of Medicine, Wayne University School of Medicine, Detroit, Michigan)

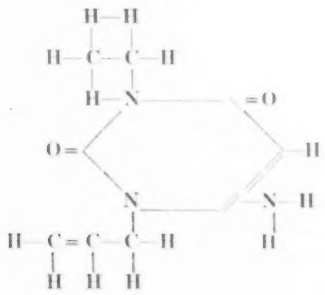
One of the major problems of clinical medicine has been the management of edema. Dietary control of sodium, the use of synthetic resins as well as the utilization of the xanthines and mercurial diuretics have been major factors in edema control. The induction of diuresis by injection of mercurial preparations is the most rapid, effective and reliable method available today. Parenteral injections, however, are not without risk. Proper medical supervision necessitates frequent clinic and office visits which are costly and time-consuming. Self administration is difficult and limited to the more intelligent patient.

In an attempt to overcome these difficulties investigators have continued to search for an oral preparation as effective as the parenteral mercurials, which could be given for long intervals without side effects. In this search a number of 1 mono and 1–3 dialkyl-6-aminouracils have been synthesized (Kattus, Newman and Franklin[6], Papesch and Schroeder[8], and Van Arman *et al.*[10]). Included in this series were two substances which appeared to possess potent diuretic properties (Greiner and Gold[3], Hellman, Altchek and Enselberg[4], Kattus, Arrington and Newman[5], Miller and Griffith[7], and Spencer and Lloyd-Thomas[9]). These were referred to as 1-propyl-3-ethyl-6-aminouracil and 1-allyl-3-6-aminouracil. Further studies revealed that each of these experimental products was a mixture of two isomers, and separation of these isomers was accomplished for the purpose of determining which of these four substances was the most efficient (Winter[11]). The single isomer thus selected was identified as 1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione (Mictine) and may be represented by the structural formula on the following page.

This preparation cannot be considered as "potent" as parenterally administered mercurial diuretics but the diuretic response obtained from its administration is in the majority of instances quite adequate. The edematous patient without salt depletion apparently responds best to its use; and it may be used without danger in edematous

*Supplied by G. D. Searle & Company, Chicago, Illinois.

states associated with liver or kidney damage, although the response in such individuals is not predictable. It produces less potassium and chloride diuresis than do the mercurials, the latter ion seemingly being excreted in equimolar proportion to sodium. It is believed to act primarily by inhibiting the reabsorption of sodium ion by the renal tubule (Dettelbach[1]). The enzyme systems involved in this action are not known; neither carbonic anhydrase nor succinic dehydrogenase are involved (Gilbert and Flack[2]).



Methods. Therapeutic trials with this preparation were undertaken in edematous hospital patients in the Cardiology Section of the Veterans Administration Hospital, Dearborn, Michigan. The criterion for selection was the presence of 3 plus pitting edema. A majority of the selected cases represented problems in edema management with little response to the usual diuretic measures.

Sixteen cases of congestive heart failure or cirrhosis with edema were studied. The patients with congestive heart failure were all receiving maintenance doses of digitalis. After a control period of 3 days on a 200 mg. sodium diet, 1.5 gm. of 1-allyl-3-ethyl-7-aminotetrahydropyrimidinedione (Mictine) was administered in three divided doses with meals for a period of 3 days. The clinical course, daily weight, intake, output, and 24-hour urine loss of water, sodium, potassium and chlorides were recorded prior to, and during the observation periods in eleven patients. Serum sodium, potassium, chloride, carbon dioxide combining power, and blood urea nitrogen were also measured in these same patients before and during drug administration. Toxic reactions and clinical improvement were also recorded.

Six additional cases including one previously treated, were placed on the same regimen but electrolyte studies were not carried out in this group. These cases were followed by 24-hour urine excretion and weight loss. Toxic symptoms were also recorded.

Results. In an attempt to evaluate the results of this investigation the diuretic index as derived by Kattus[5] was employed. However, it soon became apparent that in many of the cases diuresis was occurring in the control period as evidenced by weight loss and urinary output. This may have been more pronounced in the patients under investigation because the sodium restriction was more severe than in the groups studied by Kattus. In the latter study no attempt was made to evaluate fluid intake and water was permitted ad-lib. Water is a known diuretic and variations in intake may well influence the results obtained. In this study water was permitted as desired, but the amount was recorded. In many instances intake varied significantly from day to day despite no attempt to force or restrict fluids. This could possibly be explained by the fact that many patients become interested in their own balance studies and unconsciously ingest more fluid.

Correction for the diuresis occurring in the control period was attempted

as follows: The average weight loss per day during the test period (Table 1). The results were graded as follows: 4 pounds per day, 4 plus, 3 pounds per day, 3 plus, 2 pounds per day, 2 plus, 1 pound per day, 1 plus.

The average fluid intake per day was subtracted from the average fluid output per day during both the control and test periods. This difference was considered the corrected average fluid loss per day for both periods. The test period minus the control period was considered the average increase in fluid output while on the drug (Table 2). This was scored as follows: less than 200 ml. scored 0, 200 to 500 ml. scored 1 plus, 500 to 1,000 ml. scored 2 plus, 1,000 to 2,000 ml. scored 3 plus, and over 2,000 scored 4 plus. No change in the Kattus scoring was made for evaluating the sodium loss. With respect to sodium excretion an average daily increase while on the drug of less than 25 mEq. scored 0, 25 to 50 mEq. scored 2, 100 to 150 mEq. scored 3 and over 150 mEq. scored 4. Table 3 portrays the average sodium loss.

TABLE 1.—CORRECTION FOR DIURESIS OCCURRING IN THE CONTROL PERIOD

Heart Disease	*Av. Weight Loss per Day Control (pounds)*	*Av. Weight Loss per Day Test (pounds)*	*Av. Weight Loss per Day above Control (pounds)*
Rheumatic			
1	1/6	2 1/6	2
2***	1/6	1 7/12	1 5/12
12	0	0	0
Arteriosclerotic			
4	0	1 1/3	1 1/3
14	5/6	3	2 1/16
Hypertensive			
6	3 1/4	4	3/4
16	+ 5/6	1 5/6	2 2/3
Luetic			
15	1/6	2 1/3	2 1/6
Cor pulmonale			
5	0	+ 1/4	+ 1/4
Myocarditis			
3	1 1/3	2 1/2	1 1/6
13***			
Cirrhosis			
7	2 1/12	1 7/6	+ 65
8	1 1/3	1 3/4	5/12
9	0	+1 1/4	+1 1/4
10	1 5/6	2/3	+1 1/6
11	0	1/3	1/3
17	1/2	2 5/6	2 1/3
18	+ 1/6	1/3	1/2
			16 | 17 27
			.96 lb./day

Average weight loss during test = .96 lbs.
*** Repeat test in same patient

It is true that the above calculations do not adequately correct for the diuresis occurring in the control period since it assumes that this is a constant figure for both the test and control periods which is, of course, not correct. However, it is felt that this more adequately interprets the results and gives a more conservative evaluation of the diuresis. A comparison of the diuretic indices

TABLE 2.—AVERAGE INCREASE IN FLUID OUTPUT WHILE ON THE DRUG

Heart Disease	*Av. 24-Hour Fluid Loss Control (ml.)*	*Av. 24-Hour Fluid Loss Test (ml.)*	*Fluid Loss 24-Hour Test Minus Control Period (ml.)*
Rheumatic			
1	277	1008	731
2	413	1173	760
12	...	+ 830	...
Arteriosclerotic			
4	+ 117	802	919
14	+ 633	+ 192	441
Hypertensive			
6	+ 885	350	1235
16	+ 465	+ 145	220
Luetic			
15	+ 593	463	1056
Cor pulmonale			
5	...	...	...
Myocarditis			
3	+ 385	55	440
13***	213	1163	950
Cirrhosis			
7	93	878	785
8	+ 623	+ 1102	+ 479
9	+ 785	+ 971	+ 186
10	+ 895	+ 892	3
11	+ 405	993	1398
17	192	840	648
18	36	563	527
			16 | 9455
			590.9

Average fluid loss/day during test = 590 ml.
*** Repeat test in same patient

TABLE 3.—AVERAGE SODIUM LOSS WHILE ON THE DRUG

Heart Disease	*Av. 24-Hour Urine Sodium Control (gm.)*	*Av. 24-Hour Urine Sodium Test (gm.)*	*Urine Sodium Loss Test Minus Control Period* (gm.)	(mEq.)
Rheumatic				
1	.53	3.24	2.71	118
2***	.12	2.47	2.35	102
12	.01	.13	0.12	0.5
Arteriosclerotic				
4	1.06	1.82	0.76	33
Hypertensive				
6	.94	5.00	4.06	177
Cor pulmonale				
5	.04	.07	.03	1.3
Myocarditis	.64	1.80	1.16	50.5
3				
Cirrhosis				
7	2.22	2.82	.62	27
8	1.36	1.60	.24	1
9	.04	.02	+ .02	+ 0.8
10	.73	.29	+ .44	+19
11	.02	.55	.53	23
				12 | 415.5
				34.6

Average sodium loss/day during test = 34.6 mEq.
*** Repeat test in same patient

as calculated by the Kattus method and by the modified technique are shown below.

Kattus Index		
No. of Cases	*Index*	*Per Cent*
2	III	12.5
5	II	31.2
5	I	31.2
4	0	25.0
16		

Modified Index		
No. of Cases	*Index*	*Per Cent*
2	III	12.5
4	II	25.0
5	I	31.2
5	0	31.2
16		

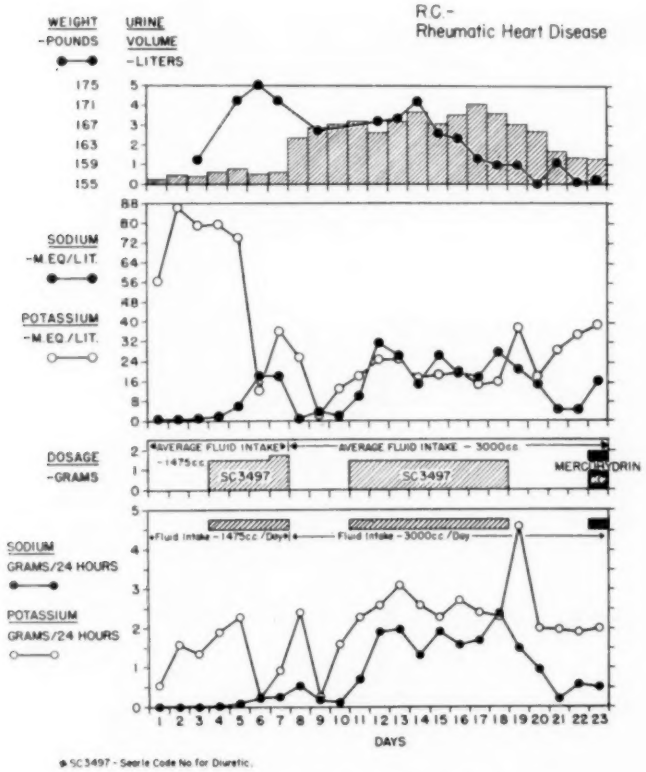


Fig. 1.—Modified diuretic index 0. Fluids forced.

Since an index of I represents an appreciable diuretic response and indices of II and above represent excellent diuresis, it is fair to state that this drug appears to have had a definite effect in 11 out of 16 cases of cirrhosis and congestive heart failure. This constitutes 68.8% of the cases treated. The average fluid loss per day was 590 ml. and the average weight loss (0.96 pounds) approximately one pound per day. These figures suggest that a 3-day course of the drug would compare favorably with one 2-ml. injection of a mercurial diuretic.

There was no excessive output of potassium nor any significant fall in serum potassium levels. Included are 3 prepared graphs illustrating the varied spectra of results observed. In one instance of rheumatic heart disease (R.C.) which failed to exhibit a diuretic response on the first course of the drug, a satisfactory diuresis was obtained when fluid intake was increased (Fig. 1). In 2 cases of cirrhosis, one of which is represented graphically (A.P.), who failed to respond to the compound on the first course, administration of the preparation with ammonium chloride produced a very satisfactory diuresis (Fig. 2.). The third chart of rheumatic heart disease (F. H.) represents a good diuretic response to the drug (Fig. 3).

With regard to the side effect produced by the drug (as indicated by nausea and vomiting), it can be said that 69% had either none or minimal reactions; 18% had a severe reaction with severe nausea, but were able to continue taking the drug; and 12% had to stop taking the drug because of nausea and vomiting.

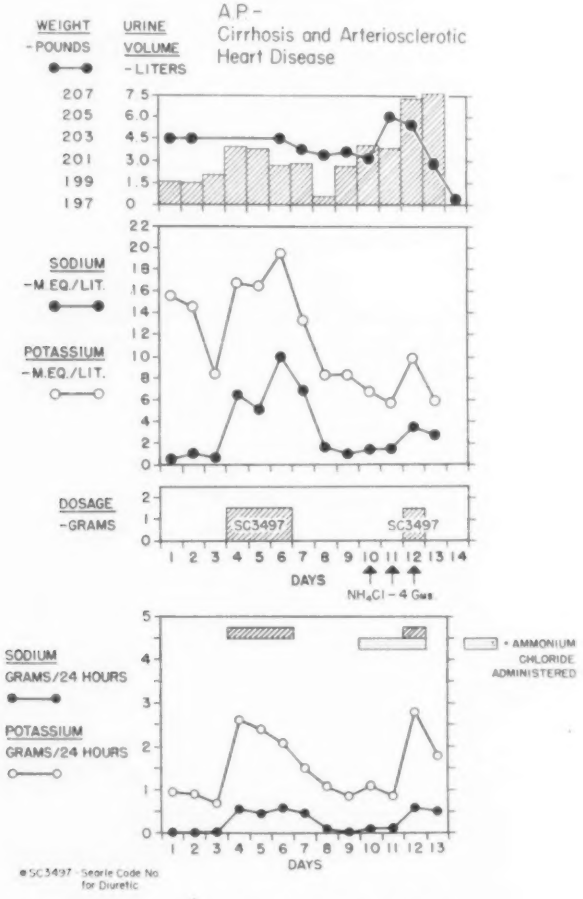


Fig. 2.—Modified diuretic index I.

Summary and Conclusion. A new

oral diuretic identified as 1-allyl-3-ethyl-6-aminotetrahydropyrimidinedione has been tested in edematous hospital cases. After an adequate control period, 1.5 gm. of the drug was administered in 3 divided doses for a period of 3 days. Eighteen therapeutic trials in 16 cases of congestive heart failure or cirrhosis were undertaken. An appreciable diuretic response was obtained as evidenced by an average daily fluid loss of 590 ml. and an average daily weight loss of approximately one pound. Side effects as indicated by nausea and vomiting were found to be present in 30% of the cases. The Kattus diuretic index was modified to more adequately grade the diuretic response in these cases and the drug was found to give an appreciable response (indices I, II or III) in 68.8% of the cases.

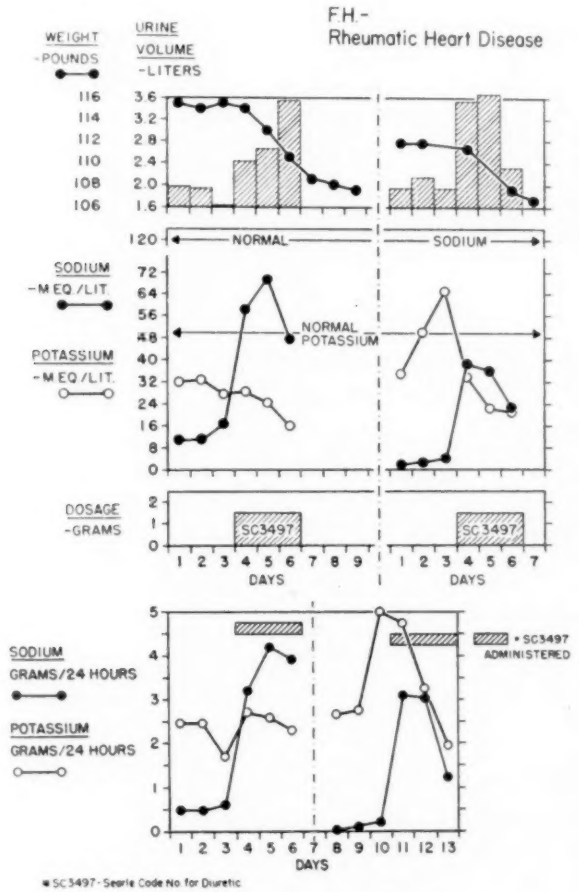


Fig. 3.—Modified diuretic index II.

The results obtained in this small series certainly suggest that the preparation possesses substantial diuretic properties, but its use is limited by the side reactions. It has been noted that repeated courses of the drug or prolonged therapy increase the tendency for nausea and vomiting to occur.

ACKNOWLEDGMENTS: Dr. I. C. Winter and the G. D. Searle & Company Research Staff assisted in providing the necessary background information on Mictine and supplied the preparation used in this study. Graphs were made by Mr. Earl C. Bartlett, medical photographer, Veterans Administration Hospital, Dearborn, Michigan. The authors are indebted to the entire Cardiology Section including the nurses, residents and ward secretaries for their assistance.

REFERENCES

1. **Dettelbach, H.:** To be published.
2. **Gilbert, R. P.,** and **Flack, H. A.:** Quart. Bull. Northwestern Med. School, **27,** 1, 1953.
3. **Greiner, T.,** and **Gold, H.:** J. Am. Med. Assn., **152,** 1130, 1953.
4. **Hellman, E., Altchek, R.,** and **Enselberg, C. B.:** Am. Heart J., **44,** 615, 1952.
5. **Kattus, A. A., Arrington, T. M.,** and **Newman, E. V.:** Am. J. Med., **12,** 319, 1952.
6. **Kattus, A. A., Newman, E. V.,** and **Franklin, J.:** Bull. Johns Hopkins Hosp., **89,** 1, 1951.
7. **Miller, H.,** and **Griffith, G. C.:** To be published.
8. **Papesch, V.,** and **Schroeder, A. F.:** J. Org. Chem., **16,** 1879, 1951.
9. **Spencer, S. G.,** and **Lloyd-Thomas, H. G.:** Brit. Med. J., **1,** 957, 1953.
10. **Van Arman, C. G., Freese, H. B., Hambourger, W. E.,** and **Green, D. M.:** Unpublished data from the Research Laboratories of G. D. Searle & Company.
11. **Winter, I. C.:** G. D. Searle & Company, Research Laboratories. Unpublished data.

SUMMARIO IN INTERLINGUA

Un Evalutation Therapeutic de 1-Allyl-3-Ethyl-6-Aminotetrahydropyrimidinediona (Mictina), un Nove Diuretico Oral

Un nove diuretico oral, identificate como 1-allyl-3-ethyl-6-aminotetrahydropyrimidinediona, esseva essayate in edematose casos hospitalisate. Post un adequate periodo de controlo, 1,5 g del droga esseva administrate in tres doses durante un periodo de tres dies. Dece-octo essayos therapeutic in 16 casos de congestive disfallimento cardiac o cirrhosis esseva interprendite. Un appreciabile responsa diuretic esseva obtenite: le perdita diurne median de fluido esseva 590 ml, e le perdita diurne median de peso esseva approximativemente un libra. Effectos lateral, manifeste per nausea e vomito, esseva notate in 30 pro cento del casos. Le indice diuretic de Kattus esseva modificate pro obtener un plus adequate gradation del responsa diuretic in iste casos. Il esseva constatate que le responsa evocate per le droga esseva appreciabile in 68,8 pro cento del casos (indices I, II, e III).

Le resultatos obtenite in iste parve serie indica certemente que le preparato possede considerabile qualitates diuretic. Nonobstante, su uso es limitate per le reactiones lateral. Esseva notate que repetite cursos del droga o su uso prolongate tende a augmentar le occurrentia de nausea e vomito.

EFFECT OF CAROTID SINUS DENERVATION ON ARTERIAL PRESSURE RESPONSE TO TETRAETHYLAMMONIUM CHLORIDE IN NORMOTENSIVE MAN

By J. W. McCubbin, M.D.

W. James Gardner, M.D.

and

Irvine H. Page, M.D.

(From the Research Division and the Department of Neurological Surgery of the Cleveland Clinic Foundation and the Frank E. Bunts Educational Institute, Cleveland, Ohio)

Section of the carotid sinus and aortic depressor nerves produces severe, chronic hypertension in laboratory animals; section of the carotid sinus nerves alone does not. The latter procedure does, however, result in pronounced increase in depressor response to TEAC (tetraethylammonium chloride), pentomethonium and hydrazinophthalazine (Page and McCubbin[3], McCubbin and Page[1]). This enhancement of depressor responsiveness in dogs led us to suggest that carotid sinus denervation might be an experimental approach to control of hypertension in those patients who do not respond adequately to depressor drugs[1]. But whether carotid sinus denervation causes enhancement of depressor responsiveness in man was not known; the present report indicates that the procedure increases depressor responsiveness to TEAC in man as it does in dogs.

Methods. Four patients were studied. The carotid sinuses were denervated in three by intracranial section of the ninth nerves and in the other by section of the sinus nerves and carotid stripping. All patients were white males, had progressive muscular dystrophy, and were 21, 14, 29 and 25 years of age; carotid sinus denervation was performed in an unsuccessful effort to confirm the report of Meurer[2] describing the beneficial effect of the procedure in this disease. The cardiovascular systems of all patients were assumed to be normal on the basis of history, physical examination, radiographic and electrocardiographic examination.

Arterial pressures were recorded with the patients supine. A Peterson catheter connected to a strain-gauge manometer was inserted through a needle into a brachial artery and a graphic record made with an ink-writing recorder. No sedation was necessary. TEAC was injected into an antecubital vein in doses of 2.5 or 1.0 mg./kg. during 3 or 4 seconds.

Result. One patient was given test doses of TEAC before and then 10 days after denervation of the carotid sinuses by intracranial section of both ninth nerves; recovery from operation had been uneventful. Figure 1 shows the responses; it will be noted that 2.5 mg./kg. of TEAC before operation caused modest falls in both systolic and diastolic pressures, more marked after the first than after the second injection as is characteristic. After intracranial section of the ninth nerves, less than one-half the previous dose of TEAC (1 mg./kg.) caused dramatic and prolonged fall in both systolic and diastolic pressures. The patient had no discomfort or apprehension during the response. Denervation of the carotid sinuses was apparently complete after intracranial section of the ninth nerves: pressure over either sinus caused fall in arterial pressure and slowing of heart

rate before operation; the same procedure caused no change in either pressure or heart rate after operation (Fig. 1).

There was no opportunity to test the other 3 patients before denervation of the carotid sinuses by section of the sinus nerve and carotid stripping in one and by intracranial section of both ninth nerves in the other two. They are included in this report because the postoperative response pattern is completely unlike the normal response. It seems reasonable, therefore, to assume it to be the result of carotid sinus denervation. Operation resulted in apparently complete denervation in all patients, for pressure over the carotid sinus caused no change in arterial pressure or heart rate. They were tested one, two and four weeks respectively after operation. Figure 2 shows the effect of repetitive doses of TEAC (1 mg./kg.) on arterial pressure in

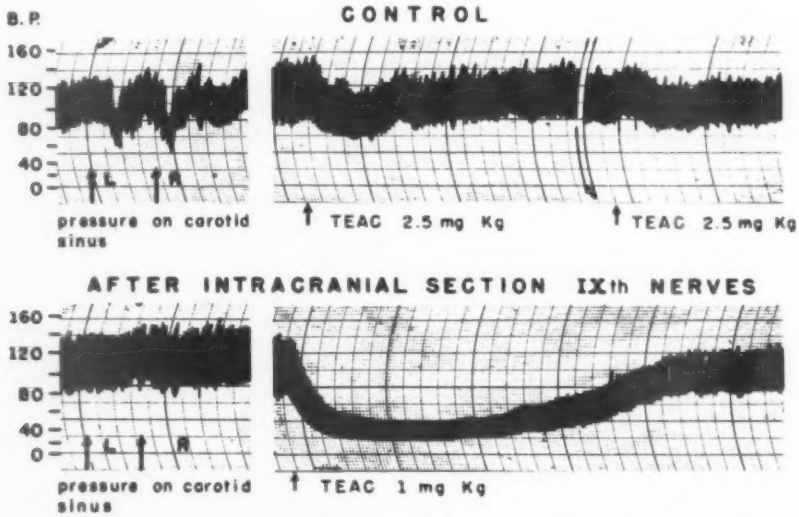


Fig. 1.—Response to TEAC much enhanced 10 days after denervation of carotid sinuses.

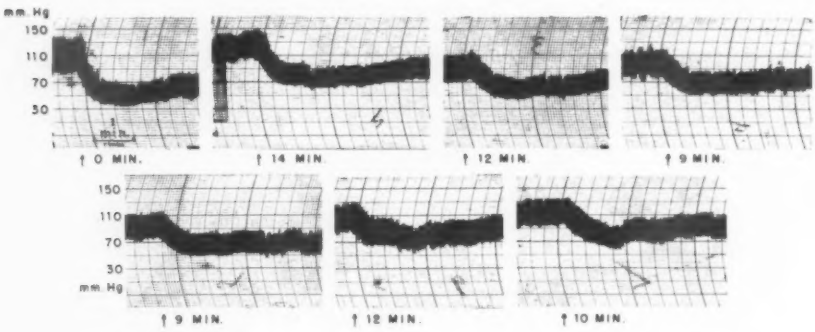


Fig. 2.—Repeated large depressor responses to TEAC (1 mg./kg.) 2 weeks after denervation of carotid sinuses. Times at arrows refer to intervals between injections.

one patient 2 weeks after denervation. Instead of usual small initial response followed by diminution and then reversal of response with repeated injections, TEAC gave repeated large depressor responses like those observed in dogs after section of the carotid sinus nerves[3]. The remaining 2 patients showed similar response patterns to repeated injections (5 and 9) of 1 or 2.5 mg./kg. of TEAC.

Summary. While denervation of the carotid sinuses does not cause significant permanent change in arterial pressure or heart rate, depressor responses to several ganglion blocking agents and hydrazinophthalazine are much enhanced in dogs[1,3]. The mechanism of this change is not clear, and the change is unexpected, since the aortic buffer reflexes are apparently competent to maintain normal blood pressure and heart rate.

The same phenomenon is found here to occur in normotensive man: responses to TEAC were much enhanced after denervation of the carotid sinuses. Change in response to TEAC in man after carotid sinus denervation is also like that in dogs in that repetitive administration of the drug elicits repeated large depressor responses instead of causing gradual diminution and then reversal of response.

REFERENCES

1. **McCubbin, J. W.,** and **Page, I. H.:** Am. J. Med. Sci., **226,** 632, 1953.
2. **Meurer, H.:** Deutsche med. Wchnschr., **75,** 753, 1950.
3. **Page, I. H.,** and **McCubbin, J. W.:** Am. J. Physiol., **168,** 208, 1952.

SUMMARIO IN INTERLINGUA

Effecto de Disnervation del Sinuses Carotide Super le Responsa del Pression Arterial a Chlorido de Tetraethylammonium in le Homine Normotensive

Durante que disnervation del sinuses carotide non causa significative cambiamentos permanente in le pression arterial o in le frequentia cardiac, illo produce in canes un multo elevate responsa al action de varie agentes ganglioblocante e de hydrazinophthalazina. Le mechanismo de iste cambiamento non es clar, e illo es inexpectate, proque le reflexos regulatori aortic es apparentemente competente a mantener normal pression sanguinee e normal frequentia cardiac.

In nostre experimentos le mesme phenomeno esseva trovate in le homine normotensive. Le responsa a chlorido de tetraethylammonium esseva multo elevate post disnervation del sinuses carotide. Le cambiamento in le responsa al droga in le homine post disnervation del sinuses carotide es etiam simile a illo de canes in le facto que repetite administrationes del droga evoca grande e repetite responsas depressori in vice de causar diminution gradual e tunc reversion del responsa.

QUANTITATION OF THE ACTIVITY OF RHEUMATOID ARTHRITIS

5. A METHOD FOR SUMMATION OF THE SYSTEMIC INDICES OF RHEUMATOID ACTIVITY

By John Lansbury, M.D.
PROFESSOR OF CLINICAL MEDICINE

(From the Department of Medicine, Temple University School of Medicine, Philadelphia, Pennsylvania)

This article brings to a conclusion a series of studies which, we believe, permit an entirely new approach to the old problem of evaluating the activity, spread and deformity in cases of rheumatoid disease. We present our findings as a basis for further study by others, emphasizing that we have outlined a method rather than a finished product.

We are well aware that our method has been applied to too few cases to permit a conclusive statement to be made as to its ultimate value or as to its range of applicability, but this is unavoidable because a thorough test of the method requires a careful analysis of data on about 50 cases proceeding to a full clinical remission over a period of many months and comparison with a comparable number of cases in which no definite trend for better or worse is apparent. Obviously this is beyond the scope of the average arthritis clinic and will require the pooling of data from numerous clinics over a considerable period of time. We, therefore, present a working model of our scheme *now*, hoping to interest others in trying it out.

About 80% of the data used in this and our previous studies come from our own hospital clinic and personal files over the last 10 years. A smaller, but crucially important series of data come from the American Rheumatism Association's Committee for the Evaluation of New Therapeutic Agents who, during 1955 (at our request as Chairman) undertook to test a clinic form for collecting statistically reliable information on rheumatoid patients receiving gold therapy. This quite extensive collective effort produced four well observed remissions as well as valuable data which made possible a statistical validation of daily salicylate intake as a measure of pain and of hemoglobin trends as a valid indicator of progressive recovery. The work of these collaborators is gratefully acknowledged below.* However, it must be made clear that this paper is not an officially sponsored report either by the above committee or by the American Rheumatism Association.

Because the etiology of rheumatoid disease is unknown, its severity (degree of activity) can only be measured *indirectly* by observing its inflammatory manifestations. These are both

*We gratefully acknowledge the work of the following doctors, who, in co-operation with the Committee for the Evaluation of New Therapeutic Agents, furnished observations on a total of 33 patients during the year 1955 for statistical analysis. Their names are hereinunder listed in alphabetical order: Drs. N. R. Abrams, B. Blumberg, R. L. Brandt, Ivan F. Duff, H. Galindez, J. L. Hollander, J. G. Mayne, W. M. Mikkelsen, Victor Pollock, Peter C. Pulos, Charles Ragan, Fred B. Rogers, Frank R. Schmid, Charles L. Short, A. J. Snyder, Irving E. Steck, Emmerson Ward, Henry A. Zevely, Morris Ziff, Jack Zuckner.

systemic and articular. Until now, rheumatologists have relied mainly on joint evaluation as a guide to assessing the activity of the disease, and, except for the sedimentation rate, the systemic manifestations of the disease have not been taken into account. Our previous studies in this series have indicated that the total extent of both joint inflammation and joint deformity can be readily summed up and expressed as a single percentile figure[3].

In this paper we shall try to show how the various systemic manifestations of rheumatoid disease can be combined to give a single index of total systemic activity. To be acceptable as an index of systemic activity, each item must be present in the majority of cases of active disease and must exhibit a statistically significant regularity of trend which correlates with the general trend of the disease. The various indices of systemic activity which

TABLE 1.—SYSTEMIC MANIFESTATIONS OF RHEUMATOID ACTIVITY

(ARRANGED IN DESCENDING ORDER OF INCIDENCE)

Index	*How Quantitated*	*Incidence*	*Average of Abnormal Findings*
1. Erythrocyte sedimentation rate	Maximum fall of RBC's in 5 minutes (Cutler)	100% of 100 cases	5.6 mm.
2. Pain on motion	Number of aspirin tablets taken per day	98% of 55 cases	8.5 tablets
3. Muscle weakness	Compression of blood pressure cuff inflated to 20 mm. Hg	98% of 100 cases	80 mm. Hg F. 120 mm. Hg M.
4. Morning stiffness	Duration after rising	97% of 100 cases	3.5 hours
5. Fatigability	Hours after rising before fatigue noted	74% of 59 cases	4.4 hours
6. Anemia	Hemoglobin below 12.2 gm. (F) and 13.4 gm. (M)	45% of 161 cases	11.2 gms.
7. Pain at rest	Hours present per day	28% of 50 cases	4.3 hours
8. Fever	Clinical thermometer	22% of 76 cases	99.4° F. 37.5° C.

The incidence of the above items and their average values were determined on the basis of observed findings at the time of the patient's first visit only. While these values provide enough information to set up a working model, confirmation based on a much larger series of observations is desirable.

Also, we have found that numerous systemic manifestations of rheumatoid activity can be objectively measured, and that, of themselves, without any reference to joint findings, they are capable of detecting a full clinical remission[1]. We have routinely recorded these systemic manifestations on our patients over a period of a year and a half and are fully persuaded as to their value as indices of the activity of the disease.

In this paper we shall try to show how the various systemic manifestations of rheumatoid disease can be combined to give a single index of total systemic activity. To be acceptable as an index of systemic activity, each item must be present in the majority of cases of active disease and must exhibit a statistically significant regularity of trend which correlates with the general trend of the disease. The various indices of systemic activity which are acceptable on the basis of the above criteria are: Anemia, ESR, Grips, Stiffness, Fatigability and Aspirin need. The incidence of these and other systemic manifestations of activity, together with their average values before treatment was instituted, are given in Table 1.

In Fig. 1, a statistical analysis (by Dr. S. M. Free, Jr.**) of the various indices of activity in patients going into remission is presented in graphic form.

**We gratefully acknowledge the invaluable work of Dr. Spencer M. Free, Jr., who carried out the statistical analyses, supervised the construction of Table 2, and gave frequent guidance regarding the mathematical aspects of the work.

In each case the trend was determined by plotting the data on semilogarithmic paper and finding the median by the method of least squares and then reconstituting the resulting curve on standard Cartesian graph paper. It will be noted that all except hours of morning stiffness decline along a straight, diagonal line. As previously pointed out[2] hours of morning stiffness decline in a concave curve. We were not able to apply the standard statistical treatment to the index of fatigability because it happened that the points of origin for each curve in the series were too close together. But, as far as could be judged, fatigability appears to follow a convex parabolic curve which is roughly the mirror image of the decline curve for hours of morning stiffness. In the case of grip-strength, a striking decline in muscle weakness occurred in too few cases for statistical analysis of the trend. However, insofar as the data can be judged, this trend also appears to follow a straight, diagonal line. (In some cases, muscular weakness appears to be irreversible and, in such instances, may be regarded as a "deformity" rather than a sign of "activity.")

We conclude that the 4 indices presented in Fig. 1 are *quantitatively related to the general trend of the systemic activity of the disease and are, therefore, reliably determinable.* It seems likely that both grip-strength and fatigability are also sufficiently reliable to be included in the list of indices, at least for the time being.

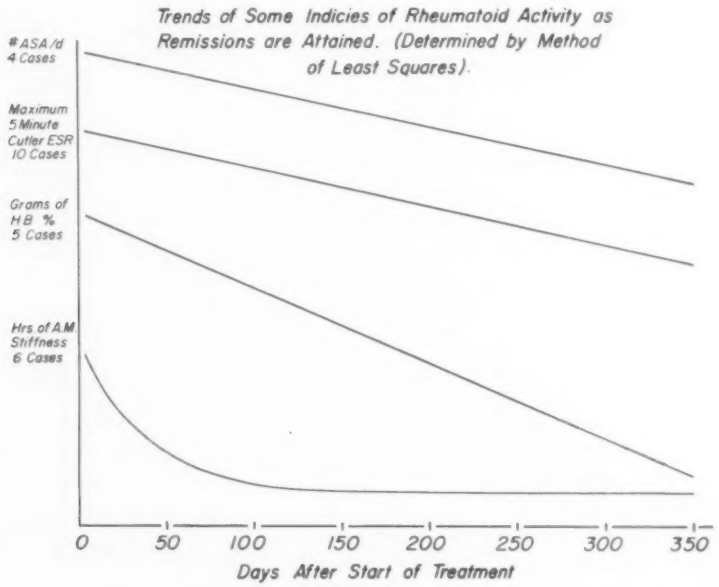


Fig. 1.—Trends of four indices of rheumatoid activity as patients go into remission. These were determined by standard biostatistical methods by Dr. S. M. Free, Jr. They indicate that the data in question can be reliably observed.

TECHNIQUE FOR OBSERVING THE INDICES. The laboratory determinations are objective and, therefore, of acceptable accuracy if properly performed.

The 5-minute maximum fall of erythrocytes as observed by the Cutler method appears to be much more reliable than the Westergren readings and therefore, if available, we recommend it, rather than the Westergren technique, for our present purpose.

In the case of measuring hand grips by compression of an inflated blood pressure cuff, it is important that the same technique be used throughout. In our cases, we have inflated the system to 20 mm. of mercury and have asked the patient to compress an ordinary (not pediatric) cuff 3 times, taking the best reading (minus 20) as our end-point and recording the average for both hands. Observations should be made at the same time of day since there may be considerable difference between morning and afternoon strength. Full co-operation by the patient is, of course, essential. These readings cannot be considered as a pure measure of muscle strength because pain in the elbow, wrist and knuckles may also give low readings. Where the grips are mechanically impaired by severe deformity or by irreversible muscle atrophy they cannot serve as a measure of "activity" and should, therefore, not be admitted to the record.

The technique for eliciting duration of morning stiffness has already been described[1,2] and presents no difficulty in the great majority of cases. In using daily aspirin consumption as an index of the severity of pain, one must be sure that the patient is taking it to relieve pain and not just from habit or because it has been previously prescribed. Likewise one must be certain that the patient is not refusing to take it because he believes it to be harmful. In the few cases where aspirin affords no relief it obviously cannot serve as an index of pain and should therefore be omitted from the record. Degrees of fatigability are judged by the number of hours of ordinary activity which the patient can undertake after rising in the morning before he feels tired. This information is more difficult to elicit, but, with diligent cross-questioning a reasonably accurate estimate can usually be made. The neurotic idlers and the compulsive workers can usually be detected and their misleading information as to fatigability withheld from the record. Fortunately they are in the minority.

In general, we may adopt the rule that no index of systemic activity which seems unreliable in a given case should be admitted to the record. The omission of one item should not seriously weaken the total index, but the rejection of two or more items reduces the basic information too drastically, and, in such cases the method must be considered inapplicable. Fortunately, our experience to date indicates that all 6 items can be reliably observed in the majority of patients.

The severity of the various indices of systemic rheumatoid activity may vary considerably from each other in individual cases. This seeming disparity probably reflects the vagaries of the rheumatoid process which predominantly affect now one and now another body function. However, the indices continue to decline in an essentially parallel fashion as the patient goes into a remission and their disparities therefore do not invalidate our efforts to sum up all these diverse manifestations of the disease.

Before describing a scheme for summing up these various indices, it is important that the reader should be reasonably certain that they are worth summing up. Otherwise the whole plan will appear futile. If we consider a hypothetical rheumatoid patient who presents all the manifestations of activity which are enumerated in Table

1, we shall agree that he has active disease, even though we are not informed as the exact status of his joints. Conversely, if 6 months later, the same patient manifests *none* (not one) of these signs and symptoms, it seems impossible that he can have any significant degree of rheumatoid activity. Whatever joint findings remain will be in the nature of asymptomatic, unresolved thickening or deformities caused by past rheumatoid activity. This does not mean that the patient does not have a hidden, smouldering tendency to rheumatoid activity lurking somewhere in his body. His rheumatoid "diathesis" is, unfortunately, still with him, awaiting only some adverse stimulus to reactivate it, even though it is not clinically detectable.

In evaluating this crucially important statement, we emphasize again that freedom from clinically significant rheumatoid activity is claimed only when *all* the indices are absent. The presence of only one index, such as an abnormal sedimentation rate, or stiffness after inactivity, indicates that the patient still has active disease and is not in full remission. On the other hand, we believe that complete absence of all the indices *does* constitute a clinical remission, provided the systemic manifestations of inflammation are not being suppressed by steroid therapy. (This does not imply that joint findings should not also be taken into account in confirming the point of full remission.)

If the foregoing be granted, and if the various indices are quantitatively observable, as we have claimed, then the possibility of combining them to form a single index of systemic rheumatoid activity seems to be a logical final step. To this we shall now address ourselves.

Certain signs and symptoms of systemic rheumatoid activity, notably fever and rest pain (adynamic joint pain), may disappear rather early as the patient recovers from the more active phases of the disease. If the other systemic manifestations of rheumatoid activity were likewise found to disappear serially as the patient goes into a remission, an Index of total systemic activity could be obtained by merely adding up the number of positive items.

Unfortunately, the various systemic manifestations of rheumatoid activity do *not* behave in this manner. Instead, our studies have shown that most of them decline in a more or less parallel fashion as the patient improves. Therefore, in order to compute an index of total systemic activity, it is necessary to record the degree of severity of each item and furthermore, to find a way of adding these together so that their total or average severity may be recorded. To do this one must find a *common denominator* for such utterly diverse things as sedimentation rate, anemia, stiffness, fatigability, muscular strength and aspirin consumption.

We believe that the value for the average degree of severity of each item obtained on the occasion of the initial examination in a series of patients who had not previously been treated provides a satisfactory common denominator. These average values are recorded in the last column in Table 1. For our present purpose the value of 100 is assigned to each average so that gradations above and below this point may be expressed as percentages.

To compute the Index of Systemic Activity, one refers to Table 2 where equivalent percentages for the full range of probable observed data are arranged for ready reference. One needs only to record the percentile value of each observation, add these and obtain their average by dividing their total by the number of items (in

TABLE 2.—TABLES FOR CONVERTING OBSERVED FINDINGS INTO PERCENTILE EQUIVALENTS

Morning Stiffness		*Fatigue After*		*Aspirin/ Day*		*Grip Weakness*			*Anemia*			*5-min. Cutler ESR*		*Westergren Sed. Rate*	
Min.	*%*	*Hrs.*	*%*	*Tabs.*	*%*	*mm.*	*M%*	*F%*	*gm.*	*M%*	*F%*	*mm.*	*%*	*mm.*	*%*
5	2	8.0	0	0	0	280	0	0	13.4	0	0	1.0	0	10	0
10	5	7.5	14	1	12	270	6	0	13.2	7	0	1.5	10	15	8
15	7	7.0	29	2	25	260	12	0	13.0	15	0	2.0	20	20	17
20	9	6.5	43	3	37	250	19	0	12.8	22	0	2.5	30	25	25
30	14	6.0	57	4	50	240	25	0	12.6	30	0	3.0	40	30	33
45	21	5.5	71	5	62	230	31	6	12.4	37	0	3.5	50	35	42
Hrs.		5.0	86	6	75	220	37	12	12.2	44	0	4.0	60	40	50
1.0	29	4.5	100	7	87	210	44	19	12.0	52	9	4.5	70	45	58
1.5	43	4.0	114	8	100	200	50	25	11.8	60	19	5.0	80	50	67
2.0	57	3.5	129	9	112	190	56	31	11.6	67	29	5.5	90	55	75
2.5	71	3.0	143	10	125	180	62	37	11.4	74	38	6.0	100	60	83
3.0	86	2.5	157	11	137	170	69	44	11.2	81	48	6.5	110	65	92
3.5	100	2.0	171	12	150	160	75	50	11.0	89	57	7.0	120	70	100
4.0	114	1.5	186	13	162	150	81	56	10.8	96	67	7.5	130	75	108
4.5	129	1.0	200	14	175	140	87	62	10.6	104	76	8.0	140	80	117
5.0	143	0.5	214	15	187	130	94	69	10.4	111	86	8.5	150	85	125
5.5	157	0.0	229	16	200	120	100	75	10.2	118	95	9.0	160	90	133
6.0	171			17	212	110	106	81	10.0	126	105	9.5	170	95	142
6.5	186			18	225	100	112	87	9.8	133	114	10.0	180	100	150
7.0	200			19	237	90	119	94	9.6	141	124	10.5	190	105	158
7.5	214			20	250	80	125	100	9.4	148	133	11.0	200	110	167
8.0	229			21	262	70	131	106	9.2	156	143	11.5	210	115	175
..	..	..	..	22	275	60	137	112	9.0	163	153	12.0	220	120	183
..	..	..	..	23	287	50	144	119	8.8	170	162	12.5	230	125	192
..	..	..	..	24	300	40	150	125	8.6	178	171	13.0	240	130	200
..	..	..	..	25	312	30	156	131	8.4	185	181	13.5	250	135	208
..	..	..	..	..	..	20	162	137	8.2	193	190	14.0	260	140	217
..	..	..	..	..	..	10	169	144	8.0	200	200	14.5	270	145	225
..	..	..	..	..	..	0	175	150	..	..	..	15.0	280	150	233
..	..	..	..	..	..	..	..	..	..	..	..	15.5	290	..	..
..	..	..	..	..	..	..	..	..	..	..	..	16.0	300	..	..

The percentile equivalents are given in the nearest whole numbers and the scales are arranged by taking the average value for each item as 100 with 0 as normal. The Westergren ESR scale is based on data furnished by Drs. Ziff, Duff and Galindez. The scale for hemoglobin values was established by taking extreme values (0 and 200%) and arranging the scale to agree.

TABLE 3.—CALCULATIONS OF THE INDEX OF ACTIVITY IN TWO CASES OF RHEUMATOID ARTHRITIS

	Case of Mr. R.T.L., Aged 61				*Case of Mrs. E.H., Aged 26*			
	1/27/55		*3/21/56*		*10/7/55*		*5/1/56*	
A. M. Stiffness	30 mins.	= 14%	0 min.	= 0%	4 hrs.	= 114%	2 mins.	= 1%
Fatigue after	2 hrs.	= 171%	8 hrs.	= 0%	0 hrs.	= 229%	8 hrs.	= 0%
A. S. A. per day	7 tabs.	= 87%	4 tabs.	= 50%	8 tabs.	= 100%	0 tab.	= 0%
Grips, mm. Hg	135 mm.	= 87%	280 mm.	= 0%	170 mm.	= 44%	250 mm.	= 0%
5 min. ESR.	7 mm.	= 120%	1.5 mm.	= 10%	9 mm.	= 160%	4 mm.	= 60%
Hemoglobin gm.	11.5 gm.	= 70%	12.8 gm.	= 22%	9.7 gm.	= 114%	12.6 gm.	= 0%
Index (av. percentage)		91%		13%		126%		10%

Both the above patients would ordinarily have been considered as being in a full clinical remission at the time of the last observation, but the Index shows that slight residual activity was present in both cases. This, we believe, is more in accord with the true state of affairs.

this case 6). This takes only a few minutes and can be done either at the time of the patient's interview or later on, at one's leisure, provided all the items have been faithfully recorded. Examples showing the method of calculation in two actual cases before and after treatment are given in Table 3.

When recording the basic data as illustrated in Table 3, it is of the greatest importance that no item should be omitted, since the absence of even one datum may invalidate the whole Index. We have found that a rubber stamp which lists all the items to be observed, and which can be impressed on the patient's record at the time of each visit, is an invaluable aid in avoiding such omissions. For collecting data germane to our present scheme, a rubber stamp as given below in Table 4 is, for the present, adequate. (Details of rest and motion pain need not be recorded.)

to be relatively static, that is, showing no constant trend for better or worse. These two groups of observations have been respectively averaged for purposes of comparison and are presented in Fig. 4. A review of these 3 charts indicates that, at least in the cases studied, the Index appears to reflect the clinical course of these two groups of patients with acceptable accuracy, and, at present there is no good reason to suppose that it would not also reflect the course of the majority of patients with rheumatoid disease with equal accuracy. As to deviations from absolute accuracy, no statement is possible because no fixed point of reference is available, or even imaginable, in a disease with clinical manifestations which vary from hour to hour, from day to day and from week to week.

In judging the soundness of the proposed scheme, a clear distinction must be made between the validity of the

TABLE 4.—RUBBER STAMP FOR RECORDING PERTINENT DATA

PAIN (REST)	HRS./24	(MOTION)	HRS./24
AM STIFFNESS	HRS.	MINS.	JELLING
ASA ON Rx	*AD LIB*	GRIPS	R L
FATIGUE AFTER	HRS.	WORK	ESR HB
INDEX OF SYSTEMIC ACTIVITY	%		

Having given what is, we hope, an intelligible description of the methods by which the Index of Systemic Rheumatoid Activity is computed, and believing each step in the process to be logically sound, we are now in a position to observe the application of this Index to a series of cases of rheumatoid arthritis.

Figure 2 depicts the decline in activity in 5 cases which attained a full, or nearly full, clinical remission. Figure 3 shows the course of 8 patients in which the activity of the arthritis was judged by ordinary clinical impressions

data themselves and the validity of the method for summing up these data. We feel sure that the methods of summation are, in principle, mathematically sound and that they could be used for summing up an entirely different set of data should these ever become available. Improvements in weighting the values for the various systemic indices and further streamlining of the values given for joint size are to be expected, but such modifications would in no way affect our underlying principles, and these, therefore, appear to be of permanent value.

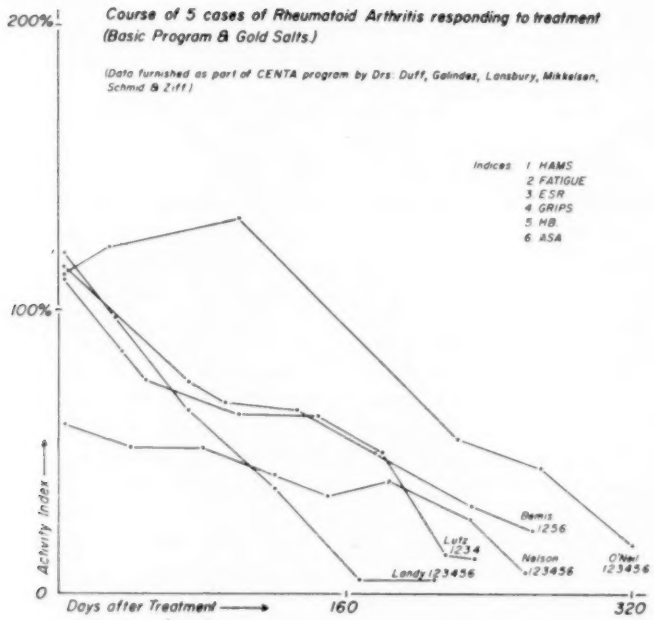


Fig. 2.—The course of 5 cases of rheumatoid arthritis proceeding to a remission under treatment with the "Basic Program" and Gold Salt Therapy as determined by the Index of Systemic Activity. In several instances the systemic manifestations showed continued rheumatoid activity even though the joint findings indicated a full remission. (Data supplied by Drs. Duff, Galindez, Lansbury, Mikkelsen, Schmid and Ziff as part of the CENTA program.)

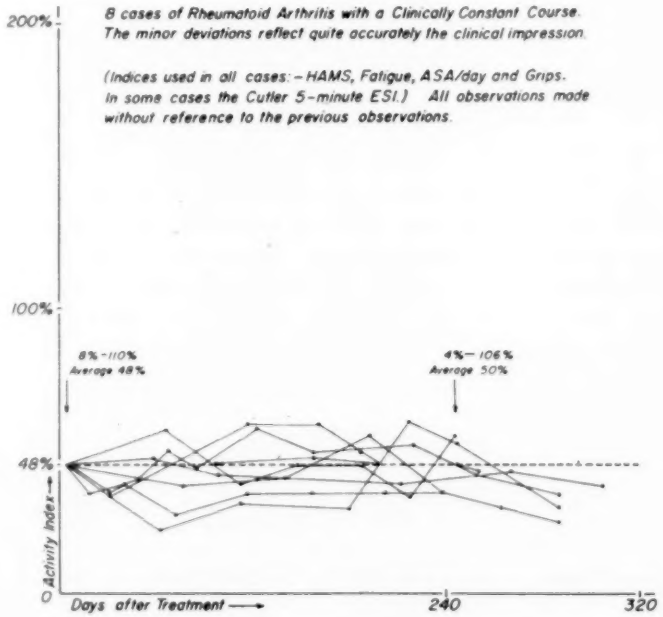


Fig. 3.—The course of 8 control cases of active rheumatoid arthritis as determined by the Index of Systemic Activity. These cases showed no definite trend for better or worse as judged by ordinary clinical methods. For purposes of comparison the starting point for each curve has been brought to the average point (48%). The trend is clearly in the direction of a straight line.

In the case of the data, both the systemic and the articular manifestations suffer from the difficulties common to the observation of all biological phenomena, but they cannot be rejected for this reason because, at present, we have nothing to put in their place. It is hoped that improved techniques for observing the various manifestations of the disease will be found and that additional indices of systemic activity will be discovered since each bona-fide Index adds to the accuracy of the final average figure. The sum of graded joint inflammation[3] might well be a valuable addition, but, for the present, we have excluded it because we are not yet convinced that gradations of joint inflammation can be objectively determined.

New laboratory methods may be eventually devised which will provide an accurate measure of rheumatoid activity, but it seems unlikely that these will ever replace clinical observations. In any case, the validity of new laboratory aids will have to be calibrated against the kind of Index which we have proposed. In the meantime, we, therefore, present our method as a workable scheme which permits us to express the essential information concerning the status of patients with rheumatoid arthritis in a quantitative manner, as follows:

CASE OF MRS. K., AGED 35. DIAGNOSIS: RHEUMATOID ARTHRITIS

Duration	1 year
Systemic Activity	80% (of average degree of activity)
Joint Involvement	51% (of total possible involvement)
Joint Deformity	9% (of total possible involvement)

(The Joint Involvement and Deformity noted above refer to the "spread" of the disease and take into account only the presence or absence of joint findings. Gradations of joint inflammation and of deformity can likewise be expressed by referring to tables given in a previous paper)[3].

Although the step by step presentation of the rationale of this method may appear complicated and tedious, its actual application, once it is grasped, is simple and practical, and takes very little time. Sooner or later this scheme will, of necessity, have to be compared with existing schemes, notably the official classification of the American Rheumatism Association which is based on the stage of anatomical derangement, the classification of functional impairment and gradations in response to therapy. This classification, which was introduced in 1949 by Steinbrocker, Traeger and Batterman[4], put an end to a long era of irresponsible therapeutic claims in the field of arthritis and provided a common language by which rheumatologists could communicate with each other concerning the status of their patients. This important first step now has an established place in the field of rheumatology.

The method which we have proposed touches on all three aspects of the above classification, but is especially concerned with response to therapy and provides, we believe, a more objective and exact determination of degrees of improvement. We hope that both methods will be tested simultaneously in the same patients so that the merits of each may be clearly and objectively established and eventually incorporated into a single official system.

Summary. In this paper, the author brings to a conclusion a series of studies on the quantitation of the activity, spread and deformity of rheumatoid arthritis.

The following systemic manifestations of the disease have been tentatively accepted as indices of rheumatoid activity because they can be observed in the majority of cases, and because a standard biostatistical evaluation of their respective trends in patients going into remission shows a regular rate of decline thus indicating that they are reliably and quantitatively observable phenomena: 1) Maximum 5-minute fall of erythrocytes by the Cutler method. 2) Grams of hemoglobin. 3) Hours of stiffness after rising in the morning. 4) Hours of ordinary activity after rising in the morning before onset of fatigue. 5) Number of aspirin tablets required per day for control of pain, and 6) strength of grips as measured by an ordinary (not a pediatric) sphygmomanometer cuff inflated to 20 mm. of mercury.

These various indices of the degree of rheumatoid activity are summed up into a Total Index of Activity by referring to a table in which percentage equivalents for the probable range of observed values is given in terms of the average values found in a large series of cases. Using this total index, the course of 5 cases proceeding to a remission is compared graphically with the course of 8 patients whose rheumatoid activity remained at a more or less constant level. From these regular but strikingly different trends, the author concludes that the Index of Rheumatoid Activity is a valid and quantitatively accurate measure of the activity of the disease.

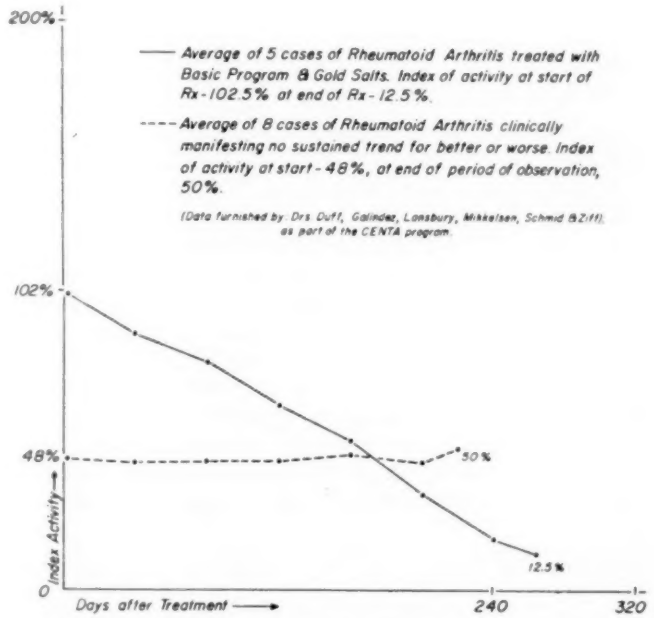

200%
Average of 5 cases of Rheumatoid Arthritis treated with Basic Program & Gold Salts. Index of activity at start of Rx - 102.5% at end of Rx - 12.5%.
Average of 8 cases of Rheumatoid Arthritis clinically manifesting no sustained trend for better or worse. Index of activity at start - 48%, at end of period of observation, 50%.
(Data furnished by Drs. Duff, Galindez, Lansbury, Mikkelsen, Schmid & Ziff, as part of the CENTA program.
102%
48%
50%
12.5%
Index Activity
0
Days after Treatment
240
320

Fig. 4.—Average of trends, as determined by the Index of Systemic Activity, of a group of 5 cases of rheumatoid arthritis proceeding to a clinical remission compared with average trend of 8 cases of rheumatoid arthritis in which the course was constant. (Data from same cases illustrated in Figs. 2 and 3.)

This Index of Activity may be used along with determinations of the per cent of possible joint inflammation and deformity (by methods previously described by the author) to provide an accurate, quantitative summary of the state of patients with rheumatoid arthritis.

REFERENCES

1. **Lansbury, J.:** Am. J. Med. Sci., **231**, 616, 1956.
2. Idem: Ibid., **232**, 8, 1956.
3. **Lansbury, J.,** and **Haut, D. D.:** Ibid., **232**, 150, 1956.
4. **Steinbrocker, O., Traeger, C. H.,** and **Batterman, R. C.:** J. Am. Med. Assn., **140**, 659, 1949.

SUMMARIO IN INTERLINGUA

Quantitation del Activitate de Arthritis Rheumatoide

5. Un Methodo pro le Summation del Indices Systemic de Activitate Rheumatoide

Con iste articulo le autor conclude un series de studios concernente le activitate, le diffusion, e le deformitates de arthritis rheumatoide.

Le sequente manifestationes systemic del morbo es tentativemente acceptate como indices de activitate rheumatoide, proque illos pote esser observate in le majoritate del casos e proque un standard evalutation biostatistic de lor tendentias respective in patientes qui entra in le phase de remission monstra un declino regular, lo que indica que illos es phenomenos de inequivoc observabilitate quantitative. (1) Maximo del reduction de erythrocytos in 5 minutas secundo le methodo de Cutler. (2) Grammas de hemoglobina. (3) Horas de rigiditate post levar se in le matino. (4) Horas de activitate routinari post levar se in le matino, ante le declaration de fatiga. (5) Numero de tablettas de aspirina requirite per die pro dominar le dolor. (6) Fortia del prisa manual, mesurate per un ordinari (non un pediatric) manchette de sphygmomanometrocon inflation a 20 mm de Hg.

Iste varie indices del grado de activitate rheumatoide es summate in un Indice Total de Activitate per referentia a un tabula in que le valores observate es convertite in le probabile equivalentias procentual super le base del valores medie trovate in un grande serie de casos. Per medio de iste Indice Total, le curso de 5 casos progredente verso un remission es comparate graphicamente con le curso de 8 casos in que le activitate rheumatoide persisteva a un nivello plus o minus constante. Ab iste regular sed frappantemente differente tendentias le autor conclude que le Indice de Activitate Rheumatoide es un valide e quantitativemente accurate mesura del activitate del morbo.

Iste Indice de Activitate pote esser usate in conjunction con determinationes del procentage del possibile inflammation e deformitate articulari (secundo methodos previemente describite per le autor) pro provider un accurate summario quantitative del stato del patiente con arthritis rheumatoide.

PROGRESS
OF
MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

G. LYMAN DUFF, M.A., M.D., PH.D., F.R.S.C., F.R.C.P.(C)
STRATHCONA PROFESSOR OF PATHOLOGY, McGILL UNIVERSITY

AND

ROGER W. REED, M.A., M.D., C.M.
PROFESSOR OF BACTERIOLOGY AND IMMUNOLOGY, McGILL UNIVERSITY
MONTREAL, CANADA

CARCINOID TUMORS

A. C. RITCHIE, M.B., CH.B.(N.Z.), D.PHIL.(OXON)

(From the Department of Pathology, Pathological Institute, McGill University, Montreal, Canada)

RATHER more than one hundred years ago, reports of tumors primary in the appendix or ileum began to appear. Some of these tumors were doubtless what are now known as carcinoid or argentaffine tumors, but the descriptions and illustrations do not permit precise pathological diagnosis. The first satisfactory description of a carcinoid tumor was given by Lubarsch[116], who in 1888 described 2 cases of "primären Krebs des Ileum." The gross description of multiple, small, whitish nodules in the submucosa and muscularis, the microscopical description of nests and strands of epithelial cells which did not resemble those of ordinary adenocarcinomata of the gut and the excellent illustrations leave no doubt that the tumors were carcinoids. The earlier report of Langhans[108] has been cited as the first description of a carcinoid tumor, but the evidence provided is insufficient to justify the diagnosis. The name "carcinoid" was introduced by Oberndorfer[144] in 1907. Tumors of the type described by Lubarsch had been called "kleine Carcinome," or "beginnende Carcinome"[143], but it was "karzinoide Tumoren" "carcinoid Tumours" which became and has remained popular.

SITE OF OCCURRENCE. Primary carcinoid tumors may arise in any part of the gastrointestinal tract from the cardia to the anus. They have been reported in the stomach, the duodenum, the jejunum, Meckel's diverticulum, the ileum, the appendix, the cecum, the colon and the rectum. They may take origin in the gallbladder and have been found in teratomata of the ovary and testis. Willis[226] gives reason for thinking that they might arise in the pancreas, but as yet no indubitable example of a carcinoid tumor primary in the pancreas has been reported. The cases reported as primary in the mesentery[6] are

probably examples of carcinoids with a small primary in the ileum, cecum or appendix and a larger secondary deposit in the mesentery.

Some adenomata of the lung are described as being of the "carcinoid type," but there is no reason to believe these are in any way related to the true carcinoid tumors[87,227].

Case Reports. From time to time, reports of cases of carcinoid tumor have been collected and tabulated. Cooke[32] listed cases of carcinoid of the small intestine published before 1931, and Ariel[3] and Dangremond[36] added to his list. Other writers have collected cases of carcinoid primary in the stomach[63,126,157], the duodenum[181], the colon[89,165], the rectum[89,133,154], Meckel's diverticulum[152], organs other than the appendix[6], malignant carcinoids[158,185,232], and malignant carcinoids primary in the appendix[88]. The best review of carcinoids of the appendix is probably still that of Simon[192].

In the present paper, no attempt has been made to search the literature to discover every report of a carcinoid tumor. However, many case reports not included in the collections cited above have been consulted, and have been used together with the cases included in the collections to calculate the statistics given in subsequent sections. To avoid burdening the text with over many references, reports not included in the collections are listed in a footnote°, and these cases together with those of the collections will be referred to as the "reference cases."

DISTRIBUTION. Most authorities agree that carcinoid tumors are found most frequently in the appendix. If the figures of thirteen reports[3,7,20,60,73,89,113,114,148,155,158,162,220] appearing between 1934 and 1954 are summed, of 509 carcinoids, 341 (67%) arose in the appendix, 117 (23%) in the jejuno-ileum, 18 (4%) in the colon, 13 (3%) in the rectum, 9 (2%) in the stomach, 5 (1%) in the duodenum, 1 (0.2%) in the gallbladder and 5 (1%) were of unknown origin. Moreover, each of these reports agrees that carcinoid tumors are found most commonly in the appendix, and that the jejuno-ileum is the next most common site of origin. In contrast, Jackman[95] reported that of 86 carcinoid tumors, only 2 arose in the appendix, and 20 in the jejuno-ileum, but that 44 took origin in the rectum.

The thirteen reports quoted above all list both surgical and necropsy cases. In five of the thirteen[3,20,60,155,158], it is possible to distinguish between the findings in surgical material and at necropsy. In the surgical material, of 196 carcinoids, 181 (92%) were found in the appendix, and 15 (8%) took origin elsewhere; but in the necropsy material, of 75 carcinoids, only 8 (11%) were primary in the appendix, while 65 (87%) arose elsewhere and 2 (3%) were of undetermined origin. Once again, the sum fairly reflects the findings of the individual reports.

Of the carcinoid tumors found in the jejuno-ileum, the majority arise in the ileum. In the thirteen reports quoted above, 117 carcinoid tumors are listed as arising in the jejuno-ileum. Of these, 77 (65%) took origin in the ileum, but only 7 (6%) in the jejunum. In 33 (28%) instances the exact site of origin was not stated. Carcinoids of the colon are also most common near the ileo-

°12 cases primary in the stomach[29,57,114,117,155,167,196,197,220,229], 10 of the duodenum[47,60,76,141,155,220], 181 of the jejuno-ileum[11,12,17,19,21,35,37,38,41,46,60,61,66,67,73,80,93,98,100,102,120,121,122,135,136,138,141,147,148,155,167,171,173,175,183,195,197,201,202,207,211,218,219,220,222,231], 8 of the colon[118,141,148,197,223], 91 of the rectum[22,60,72,79,86,95,106,140,141,148,168,176,180,190,197,205,228], 260 of the appendix[2,3,7,20,21,60,73,85,109,114,141,142,148,155,167,173,197,210], 7 of the gallbladder[8,15,28,99,178], 3 of Meckel's diverticulum[141,196], 8 of teratomata[13,62,78,127,137,191,203] and 15 of unknown origin[43,81,82,120,148,155,163,195,196,218].

cecal valve, 27 (68%) of 40 examples among the reference cases being reported as involving the cecum. Horn[89] and Ariel[3] make particular note of the frequency with which carcinoids occur in the ileo-cecal region.

It also seems that the proportion of carcinoid tumors found to be primary in the rectum is increasing. Horn[89] and Pearson and Fitzgerald[154] list only 23 cases published before 1945. Since that time at least 86 have been reported. Some of the recent reports exclude the possibility that in the past carcinoids of the rectum were recognized but not published.

MULTIPLICITY. Carcinoid tumors are often multiple. In the reference cases 28% of the carcinoids primary in the small intestine were multiple, but less than 10% of other extra-appendicular carcinoids. In the appendix, only about 1% of the cases cited were found to have multiple primaries. Primary tumors may occur in more than one part of the bowel, for example, in the ileum, cecum and appendix[114]. In most cases, the number of primary carcinoids was not great, though in one there were 68 primary carcinoids of the ileum[201], and in another "innumerable" primaries in the rectum[172].

It might be argued that the multiple carcinoids are examples of local metastases from a single primary, rather than multiple primaries. This argument cannot be refuted, but a comparison might be drawn with the multiple tumors sometimes found in endocrine glands, or in the liver. These tumors are usually accepted as multiple primaries.

INCIDENCE. Carcinoid tumors are not common. If surgical and necropsy cases are considered together, four large series give in sum an incidence of 0.08% (138 carcinoids in 175,891 cases), the range being from 0.05% to 0.20%[3,7,155,162]. In necropsied cases, the incidence varies from 0.14% to 0.34%[3,60,92,155,158], in surgical specimens from 0.06% to 0.16%[3,60,155]. Carcinoids were found in 362 (0.17%) of 214,622 appendices removed surgically, the incidence varying from 0.0% to 0.5%[20,148,192,225]. They are the most common primary tumor of the appendix[184,215], 89% of 144 examples of "primary carcinoma of the appendix" being carcinoids. From 9 to 25% of tumors of the small bowel have been found to be carcinoids[16,40,41,47,48,90,115,138], but less than 1% of "benign" tumors of the large bowel[84]. In the rectum, 5% of palpable, submucous nodules have been found to be carcinoids[86,94].

They may be found in patients of any age, from 10 days[59] to 89 years[63]. Carcinoids primary in the appendix are usually found in young people, most cases being between 10 and 30 years old[3,20,192,225,230]. In contrast, carcinoids primary elsewhere are usually found in older people, the average age of 453 reference cases being 55 years.

Carcinoids of the appendix are more common in women, 67% of 365 reference cases being women. Carcinoids which arise elsewhere are divided about equally between the two sexes, though perhaps with a slight preponderance of males.

It must be emphasized that these figures as to the incidence and distribution of carcinoid tumors are likely to be in error. For example, most carcinoids of the appendix are found in appendices removed surgically. It is highly probable that the reason why more carcinoids are not found in the appendix at necropsy is that at necropsy the appendix is rarely examined carefully in the gross, and even more rarely microscopically. The observation that carcinoid tumors of the appendix are more common in younger patients while carcinoids taking origin elsewhere occur in older people may also

be fallacious. If it be assumed that most carcinoids of the appendix produce no symptoms, then carcinoid tumors of the appendix are likely to be most common in the age group from which most appendices are removed. That is to say, carcinoid tumors of the appendix will be most common in younger people. It is, however, fair to note that some have thought that carcinoid tumors of the appendix are discovered in young people because in the little appendix the tumors soon cause appendicitis or the symptoms of appendicitis and so bring about their removal[192,210]. Carcinoids arising in larger organs only become big enough to produce symptoms after many years' growth, and so are discovered in older people. It is not only appendicular carcinoids that are likely to be overlooked at necropsy. Meissner[134] has shown how easy it is to overlook small tumors of the gastrointestinal tract. Leiomyomata of the stomach are rarely discovered at routine necropsies, and yet he found small myomata in 46% of 50 necropsies in which the stomach was examined carefully. Carcinoids of the stomach and intestine are doubtless overlooked in the same way. Again, it seems unlikely that carcinoids of the rectum are becoming more common, and yet, as is remarked above, the number of carcinoid tumors reported as primary in the rectum has greatly increased in recent years. It would seem likely that these little submucous tumors have been overlooked or, if found, misdiagnosed. For these and other similar reasons, figures as to the incidence and distribution of carcinoid tumors should only be accepted with proper reservation.

METASTASIS. For a long time, it was believed that carcinoids rarely if ever metastasized. In the paper in which he introduced the term "Karzinoid," Oberndorfer[144] makes the flat statement "Sie metastasieren nicht," and this was echoed by Forbus[59] in 1925 and even as late as 1939 by Cohn, Landy and Richter[31]. The first report of a carcinoid with metastases is probably that of Ransom, 1890[164]. By 1930, it was apparent that extra-appendicular carcinoids metastasized often[32], and as the years have passed an ever greater proportion of carcinoids has been found to metastasize. As Ariel[3] remarks, it is probable that in earlier years those carcinoids which metastasized were wrongly diagnosed as something else.

The proportion of carcinoids which metastasize varies with the site of origin. The carcinoids most likely to metastasize are those primary in the small intestine. Of the reference cases with primary in the small intestine published before 1930, 21% metastasized; of those published between 1930 and 1938, 30%; of those published between 1938 and 1942, 52%; and of those published since, 49%. Dockerty[40] in 1955 stated that 75% of his series of carcinoids of the small bowel had metastasized. Of the other reference cases, 20% of carcinoids primary in the stomach metastasized; 50% of carcinoids of the colon; and 8% of carcinoids of the rectum. Metastases have occurred from carcinoids primary in the gallbladder or Meckel's diverticulum[8,196]. Metastases from carcinoids of the appendix are rare, but do occur[2,60,73,88,109,114,192]. The most common sites of metastasis are the regional nodes and the liver, though metastatic nodules are often found in the mesentery or on the serosa near the primary. Metastases have been found in almost every organ in the body. The age and sex distribution of carcinoids with metastases do not differ from those of all carcinoids.

It is apparent that carcinoid tumors must be accepted as malignant. Although many do not metastasize, no

useful purpose is served by artificially separating them into benign and malignant forms, particularly as there is no way known in which this distinction can be made except by waiting to see if metastases develop. It is unnecessary to assume, as did Porter and Whelan[158], that there is any difference in nature between the carcinoids primary in the appendix and those which arise elsewhere. The relative infrequency of metastases from carcinoids of the appendix probably depends on some anatomical peculiarity. It has been suggested, for example, that they give symptoms early, and so are removed before they have time to establish metastases[192,210].

ASSOCIATION WITH OTHER MALIGNANT TUMORS. Pearson and Fitzgerald[155] noted that malignant neoplasms of other types were found unduly often in cases of carcinoid tumor. This impression is not confirmed by a review of the reference cases. If the carcinoids arising in the various parts of the gastrointestinal tract are considered separately, the incidence of malignant neoplasms of other types varies from 1 to 8%. These figures should be compared with the observations that 7% of 15,626 cases diagnosed as having a malignant neoplasm developed a second primary malignant tumor[221], and that up to 5% of patients with carcinoma of the large intestine develop a second primary of the intestine[206]. It should also be remembered that many carcinoids are found incidentally when exploration is undertaken because of some other neoplasm[45].

GROSS APPEARANCE. In the appendix, some 75% of carcinoids are found in the tip[114,162,192]. The appendix is usually enlarged by the tumor, though some carcinoids are too small to be seen by the naked eye[129]. On section, the tumor is classically yellow, but may be greyish-white or brown. It lies in the subepithelial fibrous tissue, and may or may not involve the muscularis. The overlying epithelium may appear intact, or the carcinoid may arise in a region in which the lumen is obliterated.

Carcinoids arising elsewhere are usually small, submucous nodules, but may be polypoid or annular and constricting[3,155]. They are often yellow, but may be white or brown[155]. The epithelium is usually intact, with the carcinoid moveable beneath it, but may be ulcerated. The tumors are usually small, but may be as large as a baby's head[20]. An occasional carcinoid may have the gross appearance of an adenocarcinoma of the usual colonic type[79]. One caused a gastro-colic fistula[118]. The muscle of the bowel wall is usually recognizable even when invaded[36]. Emphasis has been laid on the kinking of the ileum sometimes caused by a carcinoid as it spreads through the ileal wall[36,124,158], and it has been suggested that this kinking might serve as a Roentgen sign of a malignant carcinoid tumor[135].

MICROSCOPICAL APPEARANCE. The microscopical appearance of carcinoid tumors is particularly well described by Masson[71,129,130]. The description which follows is largely drawn from his papers.

When small, carcinoid tumors are confined to the subepithelial connective tissue. Routine sections often fail to show origin from the epithelium, but in a few cases continuity with the epithelium of the crypts has been demonstrated[64,116,124,155]. The tumors are made of clumps and columns of epithelial cells set in a stroma. The clumps of tumor cells are always well defined. They are usually small, but may be very large. They are usually solid without evidence of degeneration. Acinar forms occur, and occasionally a carcinoid will be predominantly acinar.

The acini may contain albuminous material or mucin[89,129]. The tumor may form pseudo-rosettes[11]. Stout[204] illustrated the "ribbon-like festoons" of tumor cells seen most often in rectal carcinoids, describing the way in which "the cells were in a single layer and the cords were bent and curled so as to resemble heaps of ribbon carelessly curled at haphazard." A single tumor may show more than one architectural pattern. Marangos[124] made a wax reconstructon of a carcinoid of the ileum and found the tumor was plexiform, the isolated islands of cells being artefacts due to sectioning. Invasion of lymphatics or blood vessels may be found in cases without metastases as well as in cases with metastases[38,124,155]. Marangos[124] found invasion of vessels in an ileal carcinoid only 1 mm. in size, and in all ileal carcinoids over 2.5 mm. in diameter. The carcinoids often invaded the vessel wall to extend in the intima, narrowing the lumen but not breaking the endothelium.

Masson[129] has divided the cells of carcinoid tumors into three types. Most common are round or polygonal cells with a central, finely reticular nucleus and cytoplasm which is moderately abundant and which may be homogeneous and acidophilic or may contain small, acidophilic granules. Small vacuoles are often present in the cytoplasm. The second type of cell is less common. They lie around the edge of the cell clumps, being called by Masson "palisade cells." Their nuclei and cytoplasm are similar to those of the first type, but the granules tend to lie in the part of the cell nearest the stroma, while the vacuoles are found around the nucleus and in the part of the cell nearest the center of the clump. Occasionally these pallisade cells are arranged as are the cells of a pseudostratified epithelium. The third type of cell is found lining small acini. They are similar to the other types, but the granules are found only in the pole distant from the lumen. The cells of the ribbon-like festoons are columnar or prismatic with elongated nuclei usually nearer one pole[204]. It should be emphasized that these forms are not distinct types, and that all intermediate forms occur. The cells of carcinoid tumors are usually remarkably uniform. Mitoses are rare. Even the large nuclei seen in adenomata of many endocrine glands are uncommon[124]. However, pleomorphic tumors do occur, with anaplastic cells, multinucleated cells, gigantic and bizarre nuclei and frequent mitoses[89,229]. These anaplastic forms do not necessarily metastasize[89].

The stroma of the tumors is often scanty, but may be abundant, even sclerosing[80,124]. It often contains muscle fibers, perhaps remnants of the hyperplastic muscularis mucosae[130]. The longitudinal and circular muscle of the intestinal wall may be hypertrophic in the vicinity of the carcinoid[41]. The stroma may contain many nerves[130], or large quantities of elastic tissue[7].

It is important to realize that the granules often found in the cells of carcinoid tumors are artefacts produced by formalin fixation[153]. Unstained, the granules are yellow[96,97]. They give the chromaffin reaction[129,145,155]. They are plumbophilic[155], and can be stained with iron hematoxylin[71]. They take up acid dyes such as eosin and acid fuchsin[129]. They give the acid and alkaline diazonium reactions[139,153,196]; Schmorl's ferric-ferricyanide reaction[153]; Gibbs' indophenol reaction[153] and, classically the argentaffine reaction, being blackened by ammoniacal silver nitrate[71,129]. They may also be stained by the techniques of silver impregnation in which a reducing agent is used[68,153]. In ultraviolet light, they show a yellow fluorescence[96,97]. In frozen sections, the vacuoles of the cells

of carcinoid tumors stain with scarlet red, Sudan IV and osmic acid, and their walls take the Ciaccio stain for phospholipid[129]. They may show doubly refractile crystals when examined by polarized light[129]. Mucin has been demonstrated by Meyer's mucicarmine stain[89]. In one carcinoid, the cytoplasm of many cells was positive to the periodic acid-Schiff sequence[57]. These histochemical findings are interpreted as indicating that the vacuoles contain a mixture of neutral fats, cholesterol esters and a little lecithin[129]. The nature of the granules has been debated. Cordier and Lison[33] thought the similar granules which appear in Kultschitzky cells fixed in formalin were phenolic, Jacobson[96,97] that they contained a pterine and a carbohydrate, Gomori[68,70] that they might contain a derivative of resorcinol and Barter and Pearse[9,10] that a fully conjugated beta-carboline derivative was present. The matter will be considered further when the secretory activity of carcinoid tumors is discussed.

The limitations of silver stains as a method of establishing a diagnosis of carcinoid tumor must be recognized. The argentaffine reaction must not be confused with those techniques of silver impregnation in which a reducing agent is used. In the argentaffine reaction, the silver salts are reduced by the reducing power of the tissue component stained. In other methods of silver impregnation, an extraneous reducing agent is provided[69,153]. Granules which give the argentaffine reaction are likely to be argyrophilic when stained by other methods, but many granules which are argyrophilic when a reducing agent is provided do not give the argentaffine reaction[153]. It is the argentaffine reaction and not argyrophilia in the presence of a reducing agent which is suggestive of a carcinoid tumor[153]. As the granules which give the argentaffine reaction are an artefact produced by fixation in formalin[129,153], the fixative employed must contain formalin. It must not contain alcohol or else the power to reduce ammoniacal silver solutions will be lost[129,153]. The tissue must be fixed within 4 to 6 hours or the tumor cells will loose their power to give the argentaffine reaction[96,129], though they may still be argyrophilic[89]. The staining technique described by Masson[129] or Gomori[68] must be followed punctiliously. As a control, it must be shown that normal Kultschitzky cells fixed in the same way will take the stain. Failure to demonstrate granules which can be blackened by the Masson or Gomori method does not mean that a tumor is not a carcinoid. Even in cases in which a suitable silver stain was used, a positive result was not always obtained[89,196,204]. Nor is a positive result unequivocal evidence that a tumor is a carcinoid, for other kinds of granule may give the argentaffine reaction[153]. Morson[139] suggested that an alkaline diazonium stain was a more satisfactory method of staining the granules of carcinoid tumors, but this reaction is not always positive either[196]. Pearse[153] discussed the value of the various methods of staining the granules, and concluded that Gibbs' reaction was the most significant. He considered that with this reaction "a negative result can probably be considered to exclude carcinoid, provided that morphologically recognizable granules are present in the cells." The importance of the condition imposed is obvious. If the diagnosis is in doubt, any histochemical findings must be interpreted with considerable care. It should also be remembered that Kultschitzky cells which give all the histochemical reactions of the cells of carcinoids have been found scattered in otherwise typical carcinomata of the stomach[132,153].

It must be emphasized that no his-

tological feature or features known enable one to distinguish those carcinoids likely to metastasize from those which will not.

HISTOGENESIS. In his paper giving the first adequate description of carcinoid tumors, Lubarsch[116] suggested that they were carcinomata arising from the crypts of Lieberkühn. Many other theories as to their histogenesis have been suggested, but now it is again believed that carcinoids are carcinomata arising from intestinal epithelium, or more precisely, from the Kultschitzky cells of the epithelium.

One of the theories popular in the early years of this century was that carcinoids arose from pancreatic rests[1,39,83,144,209], and, in particular, from islet cells of the rests[110,178,179,208]. Another view which for a time commanded some support was that carcinoids were analogous to basal cell carcinomata of the skin[23,24,104]. Some thought them endothelial sarcomata[65], or endotheliomata[101]; others that they arose from remnants of the omphalo-mesenteric duct[125,200]. A tissue malformation[119], dysontogenetic heterotopy[188], and origin from heterotropic embyronic material[50,74,161] were suggested. Ehrlich[49] thought they arose from Auerbach's plexus; Aschoff[5] that they were nevi. They were even called progonoblastomata[182]. Forbus[59] gives an excellent account of these various theories.

In 1910, Huebschmann[91] suggested that carcinoid tumors might arise from either Paneth cells or Kultschitzky cells, and in 1914 strong evidence that they indeed arose from the Kultschitzky cells was offered by Gosset and Masson. Masson[128] had shown that Kultschitzky cells contained granules which under proper conditions could be blackened by ammoniacal silver nitrate, and Gosset and Masson[71] demonstrated similar granules in two carcinoid tumors of the appendix. It had been remarked earlier by Oberndorfer[145] that both the Kultschitzky cells and the cells of carcinoid tumors gave the chromaffin reaction.

Kultschitzky cells have been called variously argentaffine cells, enterochromaffin cells, chromo-argentaffine cells, chromaffin cells, chromaphil cells, gelbe Zellen or yellow cells, basalgekörnte Zellen or basigranular cells, Nicholas cells, Schmidt cells and Ciaccio cells. They are well described by Patzelt[151] and by Ham[75]. In man, they occur in the epithelium of the gastrointestinal tract from the cardia of the stomach to the anus and in the epithelia of the biliary system and the major pancreatic ducts. They are particularly common in the crypts of Lieberkühn. They usually occur singly, lying between the other epithelial cells. They are conical or columnar, the base being applied to the basement membrane while the apex reaches towards, but not always to, the lumen. Their nuclei are usually round and regular, lying in the midpart of the cell. Their cytoplasm is clear and homogeneous, but if properly fixed shows the granules which have been mentioned previously. The granules usually lie in the base of the cell. Their staining reactions are discussed by Pearse[153].

As the years have passed, the theory that carcinoid tumors arise from Kultschitzky cells has grown ever stronger. Morphologically the cells of carcinoid tumors resemble Kultschitzky cells. The histochemical reactions of the granules of carcinoid tumors are identical with those of Kultschitzky cells[153]. The tumors have been found primary in every part of the alimentary system in which Kultschitzky cells are found except the pancreas. No carcinoid has been found primary in a site in which Kultschitzky cells are not found. In a few cases, carcinoid tumors

have been demonstrated to be continuous with an epithelium containing Kultschitzky cells[64,116,124,155]. And finally, and most convincingly, it has recently been shown that Kultschitzky cells secrete 5-hydroxytryptamine into the blood. This substance has been found in large quantity in carcinoid tumors, and in some cases is secreted by them into the blood. Its relation to carcinoid tumors will be discussed in detail hereunder.

Masson[129] elaborated the theory of origin from Kultschitzky cells, stating that argentaffine cells similar to Kultschitzky cells could be found in neuromata of the axial connective tissue of the appendix, and describing how these cells reached the nerves by a budding of the appendicular epithelium. He thought these intraneural argentaffine cells could give rise to carcinoid tumors. Papers agreeing and disagreeing with Masson's thesis are quoted by Patzelt[151]. Stout's[204] suggestion that the cells of carcinoid tumors which do not have granules may be of Erpsamer's pre-enterochrome type seems over nice.

SECRETORY ACTIVITY. The function of the Kultschitzky cells was long a matter for debate. In 1936 Patzelt[151] reviewed the literature, recounting the various suggestions put forward. Some thought the cells endocrine, some exocrine, some absorbative, some excretory. Masson and Berger[131] suggested that they emptied their secretion into nerves, forming a diffuse "neurocrine" gland, others that they played some part in the regulation of the hydrogen ion concentration in the intestine. Kultschitzky[105] himself is quoted as making, in 1896, the surprising suggestion that the cells obtained their granules from the intestine either by resorption or by the elaboration of resorbed products, and then passed the new-formed granules to leukocytes, which in this way acquired their oxyphil granules by phagocytosis. More recently, Jacobson[96,97] extended the observations of Erös and Kunos[51,52] to propose that the Kultschitzky cells played some part in normal erythropoiesis, forming a substance necessary for the prevention of pernicious anemia. Landboe-Christensen[107] and Doig and Wood[44] rebut this proposal. Another recent theory was that the Kultschitzky cells were similar to the alpha cells of the pancreas, and like them secreted glucagon, the hyperglycemic-glycogenolytic factor[224]. This hypothesis must also be rejected, for there are only superficial similarities between the alpha cells and Kultschitzky cells[77,103,216]. Weisberg and Schaefer[224] collected 690 cases of carcinoid tumor from the literature, but found blood sugar levels recorded in only 66, with evidence of hyperglycemia in 3. If it were true that carcinoid tumors arose from cells able to secrete glucagon, it would be likely that at least some of the tumors would be functional, and so would cause hyperglycemia. In the only instance Weisberg and Schaefer quote in which a carcinoid was removed from a patient with diabetes, the diabetes continued after the operation. Fein and Knudtson[57] failed to demonstrate any increase of glucagon in the blood of their patient with a carcinoid tumor of the stomach and metastases. In 7 cases of carcinoid tumor not quoted by Weisberg and Schaefer in which blood sugar levels or glucose tolerance tests are recorded, evidence of diabetes or hyperglycemia was found only in one[4,57,195,218]. Another possibility investigated was that carcinoid tumors might secrete histamine. Three carcinoids were analyzed, but contained insignificant quantities[43,167]. In 3 cases of carcinoid with metastases the histamine content of the blood was normal, and in two the histamine content of the urine was not increased[196]. In one case,

the histaminase content of the serum was normal[218]. Tumors which do secrete histamine have been reported[156], but there is no reason to think them carcinoids. A substance which affected blood pressure was extracted from a carcinoid tumor[58], but subsequent analyses were unable to confirm that there was an excess of adrenalin, noradrenalin or acetylcholine in carcinoid tissue, in the blood of patients with carcinoids or in their urine[37,167,186,218].

The demonstration that Kultschitzky cells secrete 5-hydroxytryptamine depends largely on the work of Erspamer, who for many years studied a substance he called "enteramine" which could be extracted from tissues containing Kultschitzky or similar chromaffin cells. In 1952, Erspamer and Asero[56] identified enteramine as 5-hydroxytryptamine. At the same time, other workers were studying a substance sometimes called "serotonin" which was present in blood serum. That this was also 5-hydroxytryptamine was shown by Rapport in 1949[166]. Barter and Pearse[9,10] studied the Kultschitzky cells histochemically. They were unable to demonstrate 5-hydroxytryptamine itself, but considered that the substance which appears in the cells after fixation with formalin could be formed from 5-hydroxytryptamine. Gomori[70] agreed that the histochemical reactions were consistent with the theory that Kultschitzky cells contain 5-hydroxytryptamine, and Ratzenhoffer and Lembeck[167] thought the reactions of the cells of carcinoid tumors consistent with their containing 5-hydroxytryptamine. The origin and fate of 5-hydroxytryptamine are discussed by Erspamer[53,54,55] and Page[149]. The most probable theory is that 5-hydroxytryptamine is formed from tryptophane by the Kultschitzky cells and is then secreted into the blood where it is almost all taken up by platelets. At least a large part is degraded enzymatically and excreted in the urine as 5-hydroxyindole acetic acid[53,149]. A little may escape in the urine unchanged[53]. The physiological and pharmacological actions of 5-hydroxytryptamine are discussed by Erspamer[53]. So far, it has not been established that the substance serves any physiological purpose.

That carcinoid tumors may contain large quantities of 5-hydroxytryptamine was first demonstrated by Lembeck[111,112], and his observation has been confirmed several times[37,66,150,167,195,196]. In all, 10 primary or secondary carcinoids have been analyzed, the content varying from 0.08 mcg. per gm. to 2,500 mcg. per gm. In 7 of the tumors, the content was over 200 mcg. per gm. Even in a single case the variation from tumor mass to tumor mass may be great. In one case a metastasis contained 360 mcg. per gm., though the primary contained only 61 mcg. per gm.[66], and in another the secondary contained 0.08 mcg. per gm. while the primary contained 0.33 mcg. per gm.[196]. Normally, 5-hydroxytryptamine can be detected only in the gastrointestinal system, the blood, the spleen and the central nervous system. In the gastrointestinal tract of various animals, for example, the normal content is 0.5 to 8.9 mcg. per gm.[53]. In 12 cases of carcinoid tumor with metastases, the concentration of 5-hydroxytryptamine in the serum has been found to be increased[12,37,46,66,81,156,195,196,207,214,218]. The normal concentration is given as from 0.03 to 0.4 mcg. per ml.[53,156,189,193,214]. In 11 of the cases, the concentration was from 0.4 to 15.0 mcg. per ml. and in one no figure is given. In another case with metastases, the concentration was in the normal range, varying from 0.18 to 0.22 mcg. per ml.[196]. In 5 cases of carcinoid with metastases, the urinary excretion of 5-

hydroxytryptamine was increased, being from 3 to 200 times normal[57,66,196,212]. In one case, none could be detected in the urine[218]. The urinary output of 5-hydroxyindole acetic acid has also been found increased in cases of carcinoid with metastases. The normal urinary excretion in 24 hours is from 2 to 10 mg.[53,193,194,213,214]. In 12 cases of carcinoid with metastases the urinary excretion was from 80 to 800 mg. a day[37,46,57,66,150,195]. In 3 other cases in which the output is expressed differently, there was also a marked increase[196], and one case is said to have had an increased urinary output though no figure is given[81]. The urinary output of 5-hydroxyindole acetic acid was increased in the case with metastases which had a normal serum concentration of 5-hydroxytryptamine[196]. It should be noted that some of the cases are reported in more than one of the papers cited.

The metabolism of tryptophane has been studied in patients with carcinoid tumor and metastases[195,214]. If radioactive tryptophane is fed, radioactive 5-hydroxindole acetic acid appears in the urine. In one case, the quantity of 5-hydroxyindole acetic acid in the urine varied according to the quantity of tryptophane fed, and it was found that the intake of tryptophane necessary to maintain nitrogen balance was 500 mg. a day, the normal requirement being 150 to 200 mg. a day[174]. It has even been suggested that in some cases of widespread carcinoid, pellagra has developed because almost all the available tryptophane has been converted to 5-hydroxytryptamine[34,122,195,218].

In sum, it seems probable that Kultschitzky cells secrete 5-hydroxytryptamine into the blood. It also seems likely that some carcinoids share this function, making large quantities of 5-hydroxytryptamine and secreting it in excessive quantity into the blood. This excessive secretion can be detected by determining the urinary excretion of 5-hydroxyindole acetic acid, but it should be noted that Blaschko and Hope[14] think the 5-hydroxindole acetic acid in the urine may arise in part from substances other than 5-hydroxytryptamine, and that Clerc-Bory, Pachéco and Mentzer[30] have detected it in the urine of patients with tumors of other types. It is, of course, unlikely that all carcinoid tumors produce 5-hydroxytryptamine. All islet cell tumors of the pancreas do not produce insulin, and not every pheochromocytoma is functional. To this extent, Waldenström and Ljungberg[217] are probably right in suggesting that carcinoid tumors may be of different types.

THE CARCINOID SYNDROME. In 1953, Isler and Hedinger[93] of Zürich, and Rosenbaum, Santer and Claudon[175] of Milwaukee reported a new syndrome, the essential features of which seem to be the presence of a carcinoid with metastases, a curious episodic flushing with telangiectasia of the skin, and sclerosis of the tricuspid and pulmonary valves with tricuspid insufficiency and pulmonary stenosis. Since that time, further examples of the syndrome have been published, and it has been possible to find unrecognized cases in the literature. In all 17 undoubted cases can be listed[11,19,67,80,93,98,120,136,159,163,175,183,195,207]. To these can be added 6 in which the nature of the heart disease is not so surely established[46,66,82,195,196], and 4 in which the nature of the tumor is in doubt[4,25,26,34,175]. In these 4 cases, the tumors were diagnosed as carcinomata, but in each case there is reason to believe that the tumor could have been a carcinoid. In sum, this gives 27 examples of the syndrome. The histories of 16 of the cases are summarized in the paper of Thorson, Biörck, Björkman and Walden-

ström[207]. In addition, at least 22 cases of metastatic carcinoid have been reported to have shown the curious flushing, but not the heart disease[27,41,43,57,61,98,120,122,195,196,207,218,219], and Spain[197] found at necropsy that 7 of 10 carcinoids with metastases and 3 of 16 without showed sclerosis of the valves of the right heart, though no such sclerosis was found in 500 other necropsies.

Several cases of the syndrome have been reported more than once. Waldenström and Ljungberg[218] include the cases of Thorson, Biörck, Björkman and Waldenström[207] who in turn include those of Biörck, Axén and Thorson[12]. Sjoerdsma, Weissbach and Udenfriend[195] probably include the cases they mention in other publications[193,194,214], and their Case VI seems the same as that published earlier by Daugherty, Manger, Roth, Flock, Childs and Waugh[37]. Gold and Grayzel[67] and Millman[136] describe one case, Postma[159] and Scholte[183] another.

This is not the place to mention more than briefly the clinical features of the syndrome. The flushing has been well described by several writers[25,43,195,217]. The flush starts in the face, but may extend to the chest, arms or legs. It may last up to 7 or 8 minutes. Unusual patches of cyanosis may develop in the flushed skin. The flushes may be only occasional, or may recur many times a day. In addition, the patients often develop a persistent reddish-purple discoloration of the face, looking as if they were plethoric, though the red cell count remains normal or is slightly reduced. As time passes, the patients become ever more cyanotic, and telangiectasia becomes apparent in the affected area. There is no clubbing of the fingers. The heart disease gives the expected clinical signs. Other symptoms are often associated. One of the most common is diarrhea. This often occurs as the first sign of disease, and continues throughout the course. The stool is usually described as watery. The number of motions per day is not often great, but may reach 20 or 30. Pain or borborygmi are sometimes important. In many cases, a curious asthma-like dyspnea is a troublesome and prominent symptom. The blood pressure remains normal. It is not usually altered during the attacks of flushing, but occasionally falls, in some cases precipitously[37,57,82,195,196]. Edema of the legs is often noted, even in patients who do not have heart disease. In a few cases, arthritis has been present[195].

The pathological changes in the heart are particularly well described by Hedinger and Gloor[80] and McKusick[120]. The tricuspid and pulmonary valves become vascularized and sclerotic, thickened and distorted. The sclerotic tissue may extend to form well defined cushions overlying the intima of the pulmonary artery or the endocardium of the right atrium. Sometimes it can be peeled off the underlying artery or myocardium. It may extend onto the thickened and fused cordae of the tricuspid valve. There may also be patches of endocardial fibrosis elsewhere in the right heart. The sclerotic tissue at times resembles cartilage. Microscopically, it is dense, acellular collagenous tissue with occasional collections of round cells. McKusick[120] illustrates parts of a tricuspid valve where the inflammatory reaction is more marked, and there is evidence of continuing fibroplasia. Hedinger and Gloor[80] saw no evidence of fibrin deposition, but Spain[197] found thrombotic valvulitis in one case. The end of these changes is that the tricuspid valve becomes stenotic or incompetent, the pulmonary valve funnel-like and stenotic. The mitral and aortic valves are not usually affected, though in one case in which there was a patent foramen ovale there were changes in the

mitral and aortic valves as well as in those on the right[120].

Several writers describe histological changes in the skin of patients with permanent cyanosis and discoloration of the face[4,11,98,159,175,207]. Most remark on the dilatation and congestion of veins and capillaries, several on the thickening of the vessels' walls. Jenkins and Butcher[98] remark that there was intimal thickening and narrowing in the arterioles. Arnett and Long[4], and Postma[159], thought the vessels increased in number. Bean, Olch and Weinberg[11] noted edema and chronic inflammation.

In all cases with flushing, the carcinoid tumor has had metastases. In most the liver was involved, but in one no hepatic metastases were found at necropsy[195], and in another none was evident at laparotomy[219]. Martin, Féroldi and Cabanne[127] thought involvement of the ovary important, but of the 45 cases with flushing in which the sex is given only 20 were women, and ovarian metastases are mentioned in only 7. In one case, the carcinoid may have been primary in the appendix, in the others the primary was elsewhere. The age distribution is similar to that for other carcinoids.

The relationship between the syndrome and 5-hydroxytryptamine is discussed at some length by Sjoerdsma, Weissbach and Udenfriend[195] and by Waldenström and Ljungberg[218]. In 16 of the 48 cases with flushing, evidence of excessive production of 5-hydroxytryptamine was obtained. Indeed, of the cases quoted as showing excessive quantities of 5-hydroxytryptamine in the tumor tissue, the blood or the urine, or as excreting excessive quantities of 5-hydroxyindole acetic acid, all but 5 were examples of the syndrome or suffered flushing. The exceptions are 2 cases in which tumor tissue was analyzed[111,112,167], two with an increased urinary excretion of 5-hydroxyindole acetic acid[150] and one with a high level of 5-hydroxytryptamine in the serum and excessive excretion of 5-hydroxyindole acetic acid in the urine[81]. In the first two, the symptoms were suggestive but not typical of the syndrome, in the others, no clinical information is given. It remains to consider whether the properties of 5-hydroxytryptamine are compatible with its causing the symptoms and the physical alterations of the syndrome. Pharmacological experiments on animals suggest that it could well cause the diarrhea, abdominal cramps, dyspnea and hypotension[53,149]. That it could cause the flushes and the persistent cyanosis of the face is less clear. If injected intracutaneously in man, it may produce a red reaction or a morbilliform rash[169,170]. If injected intravenously, the subject feels a tingling and burning of the face, but no flush is seen[150,198]. The injection is so unpleasant however, causing pain in the vein, abdominal and bladder cramps and hyperpnea, that it cannot be long continued. It will be noted that the abdominal and respiratory symptoms are those associated with the carcinoid syndrome. Even more difficult to explain is the sclerosis of the valves of the right side of the heart[66,195,197,207,218]. It would seem logical that it should be produced by the excessive quantity of 5-hydroxytryptamine in the blood. This is the more likely as 5-hydroxytryptamine is at least partially destroyed as it passes through the lung, so that the right side of the heart is exposed to a much higher concentration than is the left[18,199]. In one case of carcinoid with metastases, the concentration was 5.6 mcg. per ml. in the pulmonary artery, but only 0.9 mcg. per ml. in the brachial artery[66], though in three others no such difference was noted[195]. Just how 5-hydroxytryptamine could cause valvular sclerosis is quite obscure. There is

no convincing evidence that thrombosis plays an important role[80,120,197]. As the great part of the circulating 5-hydroxytryptamine is carried by the platelets[53], it might be thought that they were in some way concerned. However, Goble, Hay and Sandler[66] could find no increase in the adhesiveness of the platelets in their case, and failed to increase the adhesiveness of platelets by adding 5-hydroxytryptamine in the heparinized plasma of a control case. The observation that subcutaneously injected 5-hydroxytryptamine produces a protein-rich edema in rats may be relevant[177]. It has also been remarked in 2 cases of the syndrome, one established[80] and one probable[25,26], that there was extensive fibrosis of the pelvis, surrounding and fixing the organs as if in plaster of Paris. It may be that this is in some way similar to the sclerosis of the valves. The matter is further complicated by the large quantities of 5-hydroxytryptamine circulating in the blood of these patients. It is apparent that they must have developed a considerable tolerance. It is also necessary to remember that symptoms of the syndrome, and so presumably a high blood level of 5-hydroxytryptamine, may be present for many years[82,175,195,196,218].

Further evidence that the secretion of the carcinoid is responsible for at least some of the symptoms is given by the observations that in some cases an attack can be brought on by palpating the tumor[37,82,196], and that in others the symptoms have been relieved by partial removal of the carcinoid[37,43]. In one case traction on the tumor during surgery caused apnea[82].

Hedinger and Gloor[80] suggested that the carcinoid might be secondary to the valvular changes, rather than the valvular changes secondary to the carcinoid. This view seems scarcely tenable. Most cases of pulmonary stenosis do not develop carcinoids[34,187], and in most cases of the syndrome the heart changes develop late. Some reports even describe the evolution of the changes in the heart[66].

PROGNOSIS. Even if a carcinoid has metastasized and become inoperable, the prognosis is not necessarily bad. Carcinoids often grow very slowly. Some cases have a history of over 10 years of symptoms[43,82,175,195,196,218], and in one metastases thought to be inoperable had not grown larger when the patient died 20 years later of another cause[123].

Summary. The incidence and distribution of carcinoid tumors are discussed. Carcinoids are often multiple. The frequency with which they metastasize is noted. They do not seem associated with other neoplasms unduly frequently. Their gross and microscopical morphology is described, and their histogenesis discussed. Reason is given for thinking they arise from Kultschitzky cells. The secretory activity of carcinoids is considered, with particular reference to the possibility that they may secrete 5-hydroxytryptamine. The carcinoid syndrome (carcinoid with metastases, episodic flushing and sclerosis of the tricuspid and pulmonary valves) is described briefly, and its relationship to 5-hydroxytryptamine discussed. The prognosis in cases of carcinoid tumor is mentioned.

REFERENCES

(1) **Albrecht:** Verhandl. deutsch. path. Gesellsch., **11**, 115, 1907. (2) **Altman, V.,** and **Mann, N.:** Am. J. Surg., **76**, 434, 1948. (3) **Ariel, I. M.:** A.M.A. Arch. Path., **27**, 25, 1939. (4) **Arnett, J. H.,** and **Long, C. F.:** Am. J. Med. Sci., **182**, 212, 1931. (5) **Aschoff, L.:** München. med. Wchnschr., **57**, 1914, 1910. (6) **Ashworth, C. T.,** and **Wallace, S. A.:** A.M.A. Arch. Path., **32**, 272, 1941.

(7) **Bailey, O. T.:** Ibid., **18,** 843, 1934. (8) **Barnes, T. C.:** Surgery, **32,** 723, 1952. (9) **Barter, R.,** and **Pearse, A. G. E.:** Nature, **172,** 810, 1953. (10) Iidem: J. Path. & Bact., **69,** 25, 1955. (11) **Bean, W. B., Olch, D.,** and **Weinberg, H. B.:** Circulation, **12,** 1, 1955. (12) **Biörck, G., Axén, O.,** and **Thorson, A.:** Am. Heart J., **44,** 143, 1952. (13) **Blackwell, W. J.,** and **Dockerty, M. B.:** Am. J. Obst. & Gynec., **51,** 575, 1946. (14) **Blaschko, H.,** and **Hope, D. B.:** J. Physiol., **126,** 11P, 1955. (15) **Bosse, M. D.:** A.M.A. Arch. Path., **35,** 898, 1943. (16) **Botsford, T. W.,** and **Seibel, R. E.:** New England J. Med., **236,** 683, 1947. (17) **Bowers, C. R.,** and **Cheek, J. H.:** A.M.A. Arch. Surg., **64,** 92, 1952. (18) **Bradley, T. R., Butterworth, R. F., Reid, G.,** and **Trautner, E. M.:** Nature, **166,** 911, 1950. (19) **Branwood, A. W.,** and **Bain, A. D.:** Lancet, **2,** 1259, 1954. (20) **Bretschger, E.:** Deutsche Ztschr. Chir., **249,** 297, 1937. (21) **Brown, C. H., Bissonnette, R. B.,** and **Steele, H. H.:** Gastroenterology, **12,** 225, 1949. (22) **Buchanan, F. T., Smith, A. M.,** and **Aldrich, E. M.:** Surgery, **33,** 909, 1953. (23) **Bunting, C. H.:** Bull. Johns Hopkins Hosp., **15,** 389, 1904. (24) **Burkhardt, J. L.:** Frankfurt. Ztschr. Path., **3,** 593, 1909.

(25) **Cassidy, M. A.:** Proc. Roy. Soc. Med., **24,** 139, 1930–31. (26) Idem: Ibid., **24,** 920, 1930–31. (27) Idem: Ibid., **27,** 220, 1933–34. (28) **Christie, A. C.:** J. Clin. Path., **7,** 318, 1954. (29) **Christopherson, W. M., Higgins, J. R., McCullough, J. Y.,** and **Wolfe, N. A.:** Am. J. Surg., **86,** 224, 1953. (30) **Clerc-Bory, M., Pachéco, H.,** and **Mentzer, C.:** Compt. rend. Acad. d. Sci., **258,** 525, 1954. (31) **Cohn, S., Landy, J. A.,** and **Richter, M.:** A.M.A. Arch. Surg., **39,** 647, 1939. (32) **Cooke, H. H.:** A.M.A. Arch. Surg., **22,** 568, 1931. (33) **Cordier, R.,** and **Lison, L.:** Bull. d'Histol. app., **7,** 140, 1930. (34) **Currens, J. H., Kinney, T. D.,** and **White, P. D.:** Am. Heart J., **30,** 491, 1945.

(35) **D'Albora, J. B.,** and **Ingegno, A. P.:** Gastroenterology, **10,** 310, 1948. (36) **Dangremond, G.:** Am. J. Clin. Path. **12,** 223, 1942. (37) **Daugherty, G. W., Manger, W. M., Roth, G. M., Flock, E. V., Childs, D. S., Jr.,** and **Waugh, J. M.:** Proc. Staff Meet., Mayo Clin., **30,** 595, 1955. (38) **Dickson, J. A., Parkhill, E. M.,** and **Kiernan, P. C.:** Surg., Gynec. & Obst., **82,** 675, 1946. (39) **Dietrich, A.:** Frankfurt. Ztschr. Path., **13,** 390, 1913. (40) **Dockerty, M. B.:** Am. J. Clin. Path., **25,** 794, 1955. (41) **Dockerty, M. B.,** and **Ashburn, F. S.:** A.M.A. Arch. Surg., **47,** 221, 1943. (42) **Dockerty, M. B., Ashburn, F. S.,** and **Waugh, J. M.:** Proc Staff Meet., Mayo Clin., **19,** 228, 1944. (43) **Dockerty, M. B.,** and **Scheifley, C. H.:** Am. J. Clin. Path., **25,** 770, 1955. (44) **Doig, R. K.,** and **Wood, I. J.:** Med. J. Australia, **2,** 565, 1950. (45) **Dukes, C. E.:** Proc. Roy. Soc. Med., **39,** 763, 1945–46. (46) **Duncan, D., Garven, J. D.,** and **Gibbons, J. L.:** Brit. Med. J., **2,** 1586, 1955.

(47) **Ebert, R. E., Parkhurst, G. F., Melendy, O. A.,** and **Osborne, M. P.:** Surg., Gynec. & Obst., **97,** 135, 1953. (48) **Ehrlich, J. C.,** and **Hunter, O. B.:** Ibid., **85,** 98, 1947. (49) **Ehrlich, S. L.:** Bull. méd. de Kharkow, 1914 (quoted by **Masson**[120]). (50) **Engel, D.:** Virchows Arch. path. Anat., **244,** 38, 1923. (51) **Erös, G.:** Wien. klin. Wchnschr., **46,** 1119, 1933. (52) **Erös, G.,** and **Kunos, S.:** Ibid., **49,** 270, 1936. (53) **Erspamer, V.:** Pharmacol. Rev., **6,** 425, 1954. (54) Idem: J. Physiol., **127,** 118, 1955. (55) Idem: Triangle (Sandoz, Basle), **2,** 129, 1956. (56) **Erspamer, V.,** and **Asero, B.:** Nature, **169,** 800, 1952.

(57) **Fein, S. B.,** and **Knudtson, K. P.:** Cancer, **9,** 148, 1956. (58) **Feyrter, F.,** and **Unna, K.:** Virchows Arch. path. Anat., **298,** 187, 1936–37. (59) **Forbus, W. D.:** Bull. Johns Hopkins Hosp., **37,** 130, 1925. (60) **Foreman, R. C.:** Ann. Surg., **136,** 838, 1952. (61) **Fraser, I.:** Lancet, **2,** 174, 1955.

(62) **Gabrilove, J. L.:** A.M.A. Arch. Path., **31,** 508, 1941. (63) **Gallinaro, A. E.:** Arch. ital. chir., **69,** 239, 1947. (64) **Gáspár, I.:** Am. J. Path., **6,** 515, 1930. (65) **Glazebrook:** Virginia Med. Month., **22,** 211, 1895 (quoted by **Forbus**[59]). (66) **Goble, A. J., Hay, D. R.,** and **Sandler, M.:** Lancet, **2,** 1016, 1955. (67) **Gold, I. R.,** and **Grayzel, D. M.:** Am. J. Surg., **60,** 144, 1943. (68) **Gomori, G.:** A.M.A. Arch. Path., **45,** 48, 1948. (69) Idem: Microscopic Histochemistry. Chicago: University of Chicago Press, 1952. (70) Idem: J. Histochem. & Cytochem., **2,** 50, 1954. (71) **Gosset, A.,** and **Masson, P.:** Presse méd., **22,** 237, 1914. (72) **Green, R. E.:** Am. J. Surg., **91,** 351, 1956. (73) **Grimes, O. F.,** and **Bell, H. G.:** Surg., Gynec. & Obst., **88,** 317, 1949.

(74) **Hageman, F.**: Ztschr. Krebsforsch., **16**, 404, 1917–19. (75) **Ham, A. W.**: Histology. Philadelphia: J. B. Lippincott Co., 1950. (76) **Hannan, J. R., Hazard, J. B.**, and **Wise, R. E.**: Am. J. Roentgenol., **66**, 569, 1951. (77) **Hartroft, W. S., Wrenshall, G. A.**, and **Wilson, W. D.**: Am. J. Path., **30**, 621, 1954. (78) **Hartz, P. H.**: Am. J. Path., **21**, 1167, 1945. (79) **Haynes, L. L., Shirley, L. E.**, and **Hume, W. I.**: Surgery, **33**, 567, 1953. (80) **Hedinger, C.**, and **Gloor, R.**: Schweiz. med. Wchnschr., **84**, 942, 1954. (81) **Hegglin, R.**, and **Langemann, N.**: Personal communication to **Erspamer** quoted by him in Triangle, **2**, 136, 1956. (82) **Heimark, J. J.**, and **Parkin, T. W.**: Proc. Staff Meet., Mayo Clin., **31**, 56, 1956. (83) **Heller**: Verhandl. deutsch. path. Gesellsch., **11**, 115, 1907. (84) **Helwig, E. B.**: Surg., Gynec. & Obst., **76**, 419, 1943. (85) **Hilsabeck, J. R., Woolner, L. B.**, and **Judd, E. S., Jr.**: Am. J. Surg., **84**, 670, 1952. (86) **Hines, M. O.**, and **Ridler, J. G.**: Surgery, **29**, 496, 1951. (87) **Holley, S. W.**: Mil. Surgeon, **99**, 528, 1946. (88) **Hopping, R. A., Dockerty, M. B.**, and **Masson, J. C.**: A.M.A. Arch. Surg., **45**, 613, 1942. (89) **Horn, R. C.**: Cancer, **2**, 819, 1949. (90) **Horsley, J. S.**: J. Am. Med. Assn., **117**, 2119, 1941. (91) **Huebschmann, P.**: Rev. méd. Suisse Rom., **30**, 317, 1910. (92) **Humphreys, E. M.**: Am. J. Cancer, **22**, 765, 1934.

(93) **Isler, P.**, and **Hedinger, C.**: Schweiz. med. Wchnschr., **83**, 4, 1953.

(94) **Jackman, R. J.**: Proc. Staff Meet., Mayo Clin., **22**, 502, 1947. (95) Idem: Am. J. Surg., **88**, 909, 1954. (96) **Jacobson, W.**: J. Path. & Bact., **39**, 1, 1939. (97) **Jacobson, W.**, and **Simpson, D. M.**: Biochem. J., **40**, 3, 1946. (98) **Jenkins, J. S.**, and **Butcher, P. J. A.**: Lancet, **1**, 331, 1955. (99) **Joël, W.**: Zentralbl. allg. Path., **46**, 1, 1929. (100) **Jonsson, S. O.**: Acta chir. scandinav., **98**, 390, 1949.

(101) **Kelly**: Univ. Med. Mag. (Phila.), **13**, 160, 1900 (quoted by **Forbus**[59]). (102) **Koch, F.**: Chirurg., **12**, 270, 1940. (103) **Korp, W.**, and **LeCompte, P. M.**: Diabetes, **4**, 347, 1955. (104) **Krompecher, E.**: Beitr. path. Anat., **65**, 79, 1919. (105) **Kultschitzy, N.**: Med. Umsch. (Moskau), **46**, 90, 1896 (quoted by **Patzelt**[151]). (106) **Kunkel, W. M., Waugh, J. M.**, and **Dockerty, M. B.**: Ann. Surg., **139**, 224, 1954.

(107) **Landboe-Christensen, E.**: Am. J. Med. Sci., **223**, 182, 1952. (108) **Langhans, T.**: Virchows Arch. path. Anat., **38**, 559, 1867. (109) **Latimer, E. O.**: Am. J. Surg., **54**, 424, 1941. (110) **Lauche, A.**: Virchows Arch. path. Anat., **252**, 39, 1924. (111) **Lembeck, F.**: Nature, **172**, 910, 1953. (112) Idem: Arch. exper. Path. u. Pharmakol., **221**, 50, 1954. (113) **Lemmer, K. E.**: Surgery, **12**, 378, 1942. (114) **Lewis, D.**, and **Geschickter, C. F.**: A.M.A. Arch. Surg., **28**, 16, 1934. (115) **Likely, D. S., Lisa, J. R., Stitch, M. H.**, and **Stein, H. D.**: A.M.A. Arch. Int. Med., **82**, 206, 1948. (116) **Lubarsch, O.**: Virchows Arch. path. Anat., **111**, 280, 1888. (117) **Lützow-Holm, G.**: Acta chir. scandinav., **104**, 193, 1952–53. (118) **Lynch, R. C.**, and **Boese, H. L.**: Surgery, **38**, 600, 1955.

(119) **McCordock**: Bull. Buffalo Gen. Hosp., July, 1924 (quoted by **Forbus**[59]). (120) **McKusick, V. A.**: Bull. Johns Hopkins Hosp., **98**, 13, 1956. (121) **McLeod, C. E.**: Am. J. Clin. Path., **14**, 301, 1944. (122) **McNeely, R. D. G.**, and **Jones, N. W.**: Gastroenterology, **6**, 443, 1946. (123) **Mallory, T. B.**: New England J. Med., **222**, 686, 1940. (124) **Marangos, G. N.**: Beitr. path. Anat., **86**, 48, 1931. (125) **Marchand**: Verhandl. deutsch. path. Gesellsch., **11**, 115, 1907. (126) **Martin, J. D., Jr.**, and **Atkins, E. C.**: Ann. Surg., **31**, 698, 1952. (127) **Martin, J. F., Féroldi, J.**, and **Cabanne, F.**: Ann. d'Anat. Path., **1**, 19, 1956. (128) **Masson, P.**: Compt. rend. Acad. d. Sci., **158**, 59, 1914. (129) Idem: Am. J. Path., **4**, 181, 1928. (130) Idem: Ibid., **6**, 499, 1930. (131) **Masson, P.**, and **Berger, L.**: Compt. rend. Acad. d. Sci., **176**, 1748, 1923. (132) **Masson, P.**, and **Martin, J. F.**: Bull. Assn. franc. étude cancer, **17**, 139, 1928. (133) **Mayo, H. W.**, and **McKee, E. E.**: A.M.A. Arch. Surg., **62**, 506, 1951. (134) **Meissner, W. A.**: A.M.A. Arch. Path., **38**, 207, 1944. (135) **Miller, E. R.**, and **Herrmann, W. W.**: Radiology, **39**, 214, 1942. (136) **Millman, S.**: Am. Heart J., **25**, 391, 1943. (137) **Mitchell, N.**, and **Diamond, B.**: Cancer, **2**, 799, 1949. (138) **Morison, J. E.**: Brit. J. Surg., **29**, 139, 1941–42. (139) **Morson, B. C.**: Ann. Rept. Brit. Empire Cancer Campaign, **32**, 129, 1954. (140) **Morton, P. C.**, and **Fraser, R. W.**: Am. J. Surg., **85**, 43, 1953. (141) **Mrazek, R. G., Godwin, M. C.**, and **Mohardt, J.**: Surg., Gynec. & Obst., **96**, 661, 1953.

(142) **Nelson, M. G.**: Ulster Med. J., **8**, 179, 1939.

(143) **Oberndorfer, S.:** Verhandl. deutsch. path Gesellsch., **11,** 113, 1907. (**144**) Idem: Frankfurt. Ztschr. Path., **1,** 426, 1907. (**145**) Idem: Verhandl. deutsch. path. Gesellsch., **15,** 306, 1912. (**146**) Idem: in **Henke, E.,** and **Lubarsch, O.:** Handbuch de speziellen pathologischen Anatomie und Histologie. Berlin: Julius Springer, 1929, vol. 4/3, p. 717. (**147**) **O'Brien, J. R.:** Brit. Med. J., **2,** 1315. 1951. (**148**) **O'Sullivan, W. D.,** and **Bowie, J. J.:** A.M.A. Arch. Surg., **68,** 153, 1954.

(149) **Page, I. H.:** Physiol. Rev., **34,** 563, 1954. (**150**) **Page, I. H., Corcoran, A. C., Udenfriend, S., Sjoerdsma, A.,** and **Weissbach, H.:** Lancet, **1,** 198, 1955 with correction p. 466. (**151**) **Patzelt, V.:** in **von Möllendorff, W.** "Handbuch der mikroskopischen Anatomie des Menschen," Berlin: Julius Springer, 1936, vol. V/3. (**152**) **Pautler, E. E.,** and **Scotti, T. M.:** Gastroenterology, **17,** 88, 1951. (**153**) **Pearse, A. G. E.:** Histochemistry, Theoretical and Applied. London: J. & A. Churchill, Ltd., 1954. (**154**) **Pearson, C.,** and **Fitzgerald, P. J.:** Ann. Surg., **128,** 128, 1948. (**155**) **Pearson, C. M.,** and **Fitzgerald, P. J.:** Cancer, **2,** 1005, 1949. (**156**) **Pernow, B.,** and **Waldenström:** Lancet, **2,** 951, 1954. (**157**) **Plaut, A.:** A.M.A. Arch. Path., **28,** 712, 1939. (**158**) **Porter, J. E.,** and **Whelan, C. S.:** Am. J. Cancer, **36,** 343, 1939. (**159**) **Postma, C.:** Nederl. tijdschr. geneesk., **71,** 1842, 1927. (**160**) **Potter, E. B.,** and **Docter, J. M.:** Am. J. Path., **20,** 143, 1944. (**161**) **Primrose, A.:** Ann. Surg., **82,** 429, 1925.

(162) **Raiford, T. S.:** Am. J. Cancer, **18,** 803, 1933. (**163**) **Rambo, O. N., Jr., Gore, I.,** and **Vance, V. K.:** Am. J. Path., **30,** 625, 1954. (**164**) **Ransom, W. B.:** Lancet, **2,** 1020, 1890. (**165**) **Raphael, S. S.:** Am. J. Clin. Path., **22,** 564, 1952. (**166**) **Rapport, M. M.:** J. Biol. Chem., **180,** 961, 1949. (**167**) **Ratzenhoffer, M.,** and **Lembeck, F.:** Ztschr. Krebsforsch., **60,** 169, 1954. (**168**) **Raven, R. W.:** Proc. Roy. Soc. Med., **43,** 675, 1950. (**169**) **Reid, G.:** J. Physiol., **118,** 435, 1952. (**170**) **Reid, G.,** and **Rand, M.:** Nature, **169,** 801, 1952. (**171**) **Reynolds, R. P.,** and **Cantor, M. O.:** Am. J. Surg., **71,** 705, 1946. (**172**) **Rigdon, R. H.,** and **Fletcher, R. E.:** Ibid., **71,** 822, 1946. (**173**) **Ritchie, G.,** and **Stafford, W. T.:** A.M.A. Arch. Path., **38,** 123, 1944. (**174**) **Rose, W. C., Lambert, G. F.,** and **Coon, M. J.:** J. Biol. Chem., **211,** 815, 1954. (**175**) **Rosenbaum, F. F., Santer, D. G.,** and **Claudon, D. B.:** J. Lab. & Clin. Med., **42,** 941, 1953. (**176**) **Rosser, C.:** Surg., Gynec. & Obst., **93,** 486, 1951. (**177**) **Rowley, D. A.,** and **Benditt, E. P.:** J. Exper. Med., **103,** 399, 1956.

(178) **Saltykow, S.:** Beitr. path. Anat., **54,** 559, 1912. (**179**) Idem: Verhandl. deutsch. path. Gesellsch., **15,** 302, 1912. (**180**) **Saxe, D. H.:** Am. J. Surg., **86,** 553, 1953. (**181**) **Scamurra, V.,** and **Wiles, C. E.:** Gastroenterology, **26,** 789, 1954. (**182**) **Schoeber:** Quoted by **Masson,** Am. J. Path., **4,** 181, 1928. (**183**) **Scholte, A. J.:** Beitr. path. Anat., **86,** 440, 1931. (**184**) **Scimeca, W. B.,** and **Dockerty, M. B.:** Proc. Staff Meet., Mayo Clin., **30,** 527, 1955. (**185**) **Selberg, W.:** Virchows Arch. path. Anat., **306,** 467, 1940. (**186**) Idem: Klin. Wchnschr., **20,** 1270, 1941. (**187**) **Selzer, A., Carnes, W. H., Noble, C. A., Higgins, W. H.,** and **Holmes, R. O.:** Am. J. Med., **6,** 3, 1949. (**188**) **Semsroth K.:** A.M.A. Arch. Path., **6,** 575, 1928. (**189**) **Sharman, D. F.,** and **Sullivan, F. M.:** Nature, **177,** 332, 1956. (**190**) **Shepard, R. M., Strug, L. H.,** and **DiLeo, J. H.:** Surgery, **29,** 205, 1951. (**191**) **Simon, H. B., McDonald, J. R.,** and **Culp, O. S.:** J. Urol., **72,** 892, 1954. (**192**) **Simon, W. V.:** Ergebn. Chir. u. Orth., **9,** 291, 1916. (**193**) **Sjoerdsma, A.,** and **Udenfriend, S.:** J. Clin. Invest., **34,** 914, 1955. (**194**) **Sjoerdsma, A., Weissbach, H.,** and **Udenfriend, S.:** J. Am. Med. Assn., **159,** 397, 1955. (**195**) Iidem: Am. J. Med., **20,** 520, 1956. (**196**) **Snow, P. J. D., Lennard-Jones, J. E., Curzon, G.,** and **Stacey, R. S.:** Lancet, **2,** 1004, 1955. (**197**) **Spain, D. M.:** Am. J. Med., **19,** 366, 1955. (**198**) **Spies, T. D.,** and **Stone, R. E.:** J. Am. Med. Assn., **150,** 1599, 1952. (**199**) **Starling, E. H.,** and **Verney, E. B.:** Proc. Roy. Soc., **B97,** 321, 1925. (**200**) **Sternberg:** Verhandl. deutsch. path. Gesellsch., **11,** 116, 1907. (**201**) **Stevenson, W. O.,** and **Blanchard, A. J.:** Canad. Med. Assn. J., **51,** 259, 1944. (**202**) **Stewart, I. S.,** and **Thomson, G. R.:** Brit. Med. J., **2,** 1316, 1951. (**203**) **Stewart, M. J., Willis, R. A.,** and **de Saram, G. S. W.:** J. Path. & Bact., **49,** 207, 1939. (**204**) **Stout, A. P.:** Am. J. Path., **18,** 993, 1942.

(205) **Tavenner, M. C., Bacon, H. E.,** and **Peale, A. R.:** J. Internat. Coll. Surgeons. **16,** 265, 1951. (**206**) **Thomas, J. F., Dockerty, M. B.,** and **Waugh, J. M.:** Cancer, **1,** 564, 1948. (**207**) **Thorson, Å., Biörck, G., Björkman, G.,** and **Walden-**

ström, J.: Am. Heart J., **47**, 795, 1954. (**208**) **Toenniessen, E.**: Ztschr. Krebsforsch., 8, 355, 1910. (**209**) **Trappe, M.**: Frankfurt. Ztschr. Path., **1**, 109, 1907. (**210**) **Tuovinen, P. J.**: Ann. Chir. et gynaec. Fenniae, **35**, 169, 1946. (**211**) **Tuta, J. A.**: Illinois Med. J., **87**, 200, 1945. (**212**) **Twarog, B. M.**, and **Page, I. H.**: Am. J. Physiol., **175**, 157, 1953.

(213) **Udenfriend, S., Titus, E.**, and **Weissbach, H.**: J. Biol. Chem., **216**, 499, 1955. (**214**) **Udenfriend, S., Weissbach, H.**, and **Sjoerdsma, A.**: Science, **123**, 669, 1956. (**215**) **Uihlein, A.**, and **McDonald, J. R.**: Surg., Gynec. & Obst., **76**, 711, 1943.

(216) **Volk, B. W., Lazarus, S. S.**, and **Goldner, M. G.**: A.M.A. Arch. Int. Med., **93**, 87, 1954.

(217) **Waldenström, J.**, and **Ljungberg, E.**: Acta med. scandinav., **152**, 293, 1955. (**218**) Iidem: Ibid., **152**, 311, 1955. (**219**) **Waldmann, E. B., Martin, W. J.**, and **Ferris, D. O.**: Proc. Staff Meet., Mayo Clin., **30**, 127, 1955. (**220**) **Warren, K. W.**, and **Coyle, E. B.**: Am. J. Surg., **82**, 372, 1951. (**221**) **Watson, T. A.**: Cancer, **6**, 365, 1953. (**222**) **Watz, C. E.**: Minnesota Med., **28**, 558, 1945. (**223**) **Waugh, J. M.**, and **Snyder, J. M.**: Ann. Surg., **114**, 151, 1941. (**224**) **Weisberg, H. F.**, and **Schaefer, G. L.**: Am. J. Clin. Path., **22**, 1169, 1952. (**225**) **Weiss, G. N.**, and **Hertzog, A. J.**: Surgery, **30**, 657, 1951. (**226**) **Willis, R. A.**: Med. J. Australia, **2**, 400, 1940. (**227**) Idem: Pathology of Tumours. London: Butterworth & Co., Ltd., 2nd ed., 1953. (**228**) **Wilson, H.**: A.M.A. Arch. Path., **48**, 187, 1949. (**229**) **Wirts, C. W.**, and **Breckenridge, R. L.**: Gastroenterology, **12**, 682, 1949. (**230**) **Woolner, L. B.**: Proc. Staff Meet., Mayo Clin., **28**, 17, 1953. (**231**) **Wrightson, P.**: Brit. J. Surg., **36**, 215, 1948–49. (**232**) **Wyatt, T. E.**: Ann. Surg., **107**, 260, 1938.

SUMMARIO IN INTERLINGUA

(See page 265 for original article)

Determinationes Ventilatori e Pulmono-Voluminari in Patientes con Deformitates Thoracic

Esseva observate in septe patientes con deformitates thoracic un reduction del valores del maximal capacitate respiratori e del capacitate vital. In patientes con kyphoscoliosis e morbo de Marie-Strümpell, tanto le capacitate vital como etiam le maximo del capacitate respiratori es reducite. In comparation con normal predicibile valores, le plus frappante effecto es le reduction del capacitate vital e del total capacitate pulmonar. Iste constatation es associate con un augmento del proportion de volumine residue a total capacitate pulmonar. Le explication de isto debe esser le reduction del capacitate vital proque le volumine residue es proxime a valores normal. Iste phenomeno es probabilemente debite al limitation del expansion thoracic que es causate per le deformitates in question.

Datos obtenite per altere methodos in un gruppo de patientes kyphoscolitic se correlationa ben con le parve volumine pulmonar que es visualisate in examines radiographic e in necropsias. Patientes con kyphoscoliosis e morbo de Marie-Strümpell exhibi un reduction del capacitate inspiratori, del reserva expiratori, e del volumines residue. In le duo patientes in qui le valores esseva le plus marcatemente reducite, etiam le reserva expiratori es marcatemente reducite. Nos opina que in le curso del progresso del morbo, iste portion del volumine pulmonar pote quasi disparer. Iste basse reserva expiratori, juncte al quasi normal volumine residue, resulta in un parve functional capacitate residue que pote esser le explication del exceptionalmente basse indices de mixtion intra-pulmonar trovate per nos.

Le anormalitates constatate per nos es characterisate per un reduction del total volumine pulmonar debite al reducite expansibilitate del pariete thoracic con un associate restriction respiratori.

PREVENTIVE MEDICINE AND EPIDEMIOLOGY

UNDER THE CHARGE OF

JOHN E. GORDON, M.D.

PROFESSOR OF PREVENTIVE MEDICINE AND EPIDEMIOLOGY
HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH

AND

THEODORE H. INGALLS, M.D.

HARVARD UNIVERSITY SCHOOL OF PUBLIC HEALTH
ASSOCIATE PROFESSOR OF EPIDEMIOLOGY
BOSTON, MASSACHUSETTS

THE COMMUNITY PROBLEM IN CORONARY HEART DISEASE: A CHALLENGE FOR EPIDEMIOLOGICAL RESEARCH*

BY DAVID C. MILLER, M.D.†

FREDRICK J. STARE, M.D.

PAUL DUDLEY WHITE, M.D.

AND

JOHN E. GORDON, M.D.

(From the Departments of Epidemiology and Nutrition, Harvard University School of Public Health and the Massachusetts General Hospital, Boston, Massachusetts)

To realize that the first cause of death in the United States is a disease little known 50 years ago comes as something of a surprise to physicians and public alike. The dramatic form of coronary heart disease dates from 1912 when James B. Herrick[89] first described the clinical manifestations of coronary thrombosis with cardiac infarction. The precipitate rise of the disease to the place it now occupies is unique. Plague and other diseases from time to time have suddenly dominated a situation, but briefly. Malaria and tuberculosis ordinarily have a long history as first problems of a community, a situation sometimes reaching into antiquity and changing slowly under the impact of an improved medical practice and a developing prevention. No disease has ever come so quickly from obscurity to the place coronary heart disease now occupies, to maintain itself there with a permanence presumably to endure in this country for years to come.

Coronary heart disease was of course no newcomer among diseases of man. Much existing information was soon fitted together. Angina pectoris had been known for many years but greatly underestimated as to frequency. Thrombosis of coronary arteries had been described at necropsy, but clin-

*This study is a part of continuing investigations on atherosclerosis and coronary heart disease supported in part by the Albert and Mary Lasker Foundation, New York, New York, and the John A. Hartford Memorial Fund.

†Surgeon, U.S. Public Health Service.

ically was looked upon as an uncommon cause of sudden death, scarcely a disease which patients might survive many years. Clinical progress was rapid. Coronary heart disease is today so well known to physicians that diagnosis is among the more reliable where clinical recognition cannot be confirmed by identification of a specific agent. Because the public is also well informed, recognition at least of the manifest disease is satisfactorily early.

Treatment in the main is straightforward; on the other hand a practical prevention is scarcely past a beginning. If management and control are to improve, more must be known of causative factors. One approach is through better definition of pathogenesis; and the means are mainly through the experimental laboratory, soundly backed by clinical study. Such investigation has been active in recent years.

Atherosclerosis of the coronary arteries has been placed definitely as an integral part of the disease; of itself, however, it does not account for the completed clinical and pathological event. Increased blood pressure is recognized as an aggravating factor, but with an irregular association that leaves its role in pathogenesis ill-defined. Thrombosis of one or more coronary arteries is a usual observation at necropsy of patients dying of coronary heart disease and yet the mechanisms are not much known.

A second approach to knowledge of causative factors is through greater familiarity with the natural history of the disease. Identification of those causes having their origin in characteristics of the human host and in the environment in which man lives is the special province[76c] of the epidemiologic method. Field investigation has still other contributions to make.

Frequency distributions in populations by time, place and person repeatedly have directed laboratory or other study to the likely place to look for unknown causative factors including a specific agent, from the Devonshire Colic[12] of 1724 to arthropod-borne virus encephalitis[85] in the United States; and still later although less successfully for hemorrhagic fever in Korea[67]. This is one of the more practical contributions of field epidemiology.

In addition, communicable diseases, nutritional deficiencies and others have come under control through procedures derived wholly from observed behavior of a disease in nature. Mosquito control of yellow fever[192] antedated discovery of the virus by many years, and scurvy[163] became a preventable disease long before vitamins were known.

The search for causative factors through epidemiologic investigation is directed by choice to the whole of a disease process, all cases within a population. That includes inapparent disease and atypical forms sometimes not regularly included within the recognized entity; indeed they many times never progress to that state, and yet are inevitable precursors of the completed process. The definitive stages of a disease from beginning to end result determined quantitatively according to divisions of a population constitute a biologic gradient of disease[76b].

Biologic Gradient. In its practical application the primary separation of a chosen population is into two main segments, one with and the other without the disease, this at a specified time. Gradations expectedly exist within each of the two major divisions. Persons within the unaffected group include some who will never contract the disease because of high grade resistance, and others who are extremely likely to do so; and of course intermediates biologically susceptible but in limited degree, so that environ-

mental and other factors are more likely to decide the issue than qualities of the host. As in biology generally, no sharp line divides the sick from the well; separation is rather by a band or zone where those of low grade health merge with the slightly ill. Existing methods rarely permit sharper differentiation.

The second major division of a population, those ill with the particular disease, is also as a rule susceptible to subdivision, sometimes in clear-cut fashion as with meningococcal infection, and sometimes with much indefiniteness, as is the case with coronary heart disease. Exceptionally a disease such as rabies in man has no gradient; the course is uniform and the results identical. At any rate separations are made on the basis of clinical or laboratory measurements, most effectively and often necessarily by both, as with diphtheria[76b] for example, or pellagra[78].

By survey of a general population, by examination of an institutional or hospital population, or any other group as circumstance dictates, individuals are arranged in the separate categories to give a quantitative concept of distributions of the disease in that population. Costs are measured for each class in terms of simple disability, of permanent defect or crippling, and of deaths. Classes are compared according to frequency distribution, and kind and degree of effect. Search then proceeds for factors acting to produce the observed differences. The procedure is a prevalence study and serves also for contemporary comparison of the situation at hand with that in other localities or in other populations of the same locality.

Disease of communities, like disease in the individual, is a dynamic phenomenon. Comparison of results through serial observations on a fixed population serves to demonstrate changes in frequency and behavior, the shifts brought on by an altered environment which include among other things the introduction of preventive measures or institution of a new method of treatment. One subdivision of the gradient enlarges at the expense of another; individuals within a group move from one class to another in accordance with a progressive or a reversible pathologic process. Some individuals maintain a fixed position. The critical consideration is the causes of such movements, for groups and for individuals. Figure 1 represents the altered biologic gradient of diphtheria under the influence of immunization with diphtheria toxoid.

The total disease complex of which coronary heart disease is the advanced component is here termed atherosclerotic coronary disease, a continuum which encompasses both subclinical and clinical forms. A model to represent the impact of atherosclerotic coronary disease on a population of people has as its first element that major group judged free from the disease. Some degree of coronary atherosclerosis is clearly a feature of normality so far as man in an industrial civilization is concerned; it progresses to a point where it is recognized as pathological, as coronary arterial disease. Clinical method does not suffice to distinguish the two; neither does it permit certain recognition of even advanced coronary arterial disease, for the course is regularly subclinical and asymptomatic. Dependence at present is on demonstration at necropsy of significant narrowing of the lumen of arteries by sclerotic changes of intima and subintima.

Pathologic anatomy is likewise the final criterion for those forms recognized as coronary heart disease, which include myocardial infarction, angina pectoris and myocardial ischemia as demonstrated by electrocardiograph.

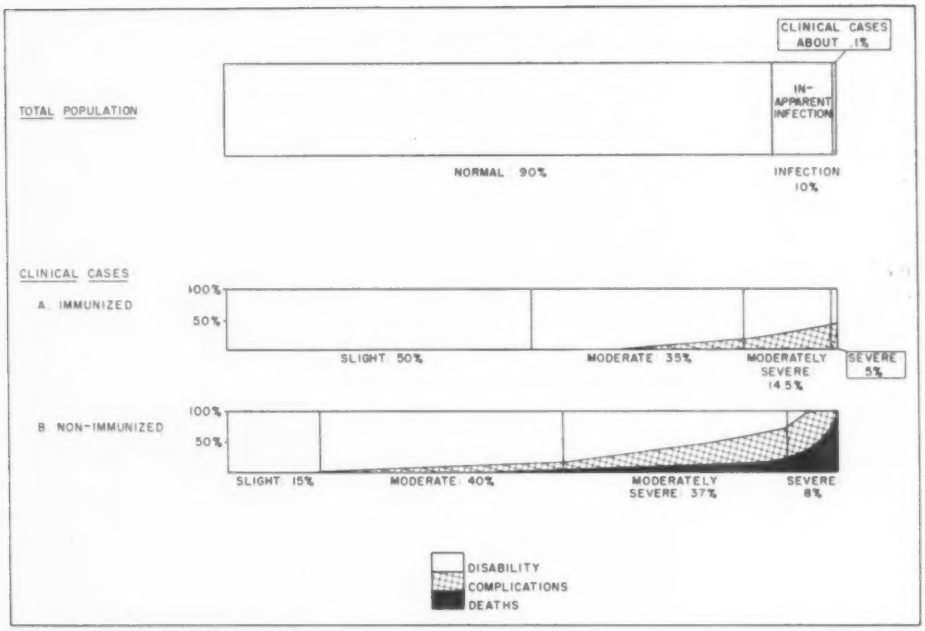


Fig. 1.—Diphtheria in immunized and non-immunized persons, Copenhagen Denmark, 1944; estimated population: 895, 815; about 50% were immunized; one-third of cases from immunized, two-thirds from non-immunized persons. *Source:* Gordon, J. E.[76b]

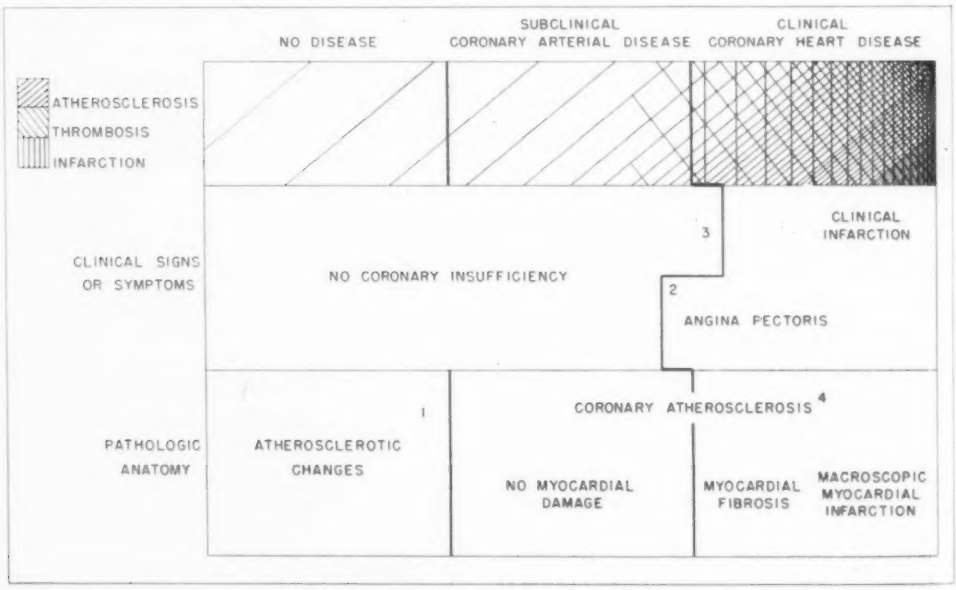


Fig. 2.—Biologic gradient of atherosclerotic coronary disease for a population, schematic and non-quantitative. *Notes:* 1. Atherosclerotic changes normal for the population. 2. Clinical angina or electrocardiographic changes of ischemia, usually without thrombosis, but not always and no myocardial damage. 3. Myocardial damage, with or without thrombosis, clinically unrecognizable. 4. Pathologic atherosclerosis with variable narrowing of lumen.

The progression pathologically is from narrowed arteries to thrombosis to infarction of heart muscle. Some individuals never experience symptoms of coronary heart disease during life and yet at necropsy present significant coronary atherosclerosis along with areas of myocardial fibrosis from old infarction; the condition is clearly coronary heart disease. Angina pectoris occurs with no symptomatic evidence of infarction. At necropsy of such patients Blumgart *et al.*[22] observed no gross infarction but double the number of major thromboses present in patients who died of clinical myocardial infarction. The mechanism protecting against infarction was judged to be a functioning collateral circulation. However, recent work[186] suggests that infarction is as common as thrombosis.

Pathologic and clinical observations thus do not coincide precisely; clinical coronary heart disease does not include all instances of myocardial damage; coronary insufficiency exists with no myocardial damage, wholly due to narrowed lumen in the presence of excess demand. These relationships are presented diagrammatically in Fig. 2 with no attempt at quantitation.

The refinement of such a pattern to the point of usefulness in epidemiologic study calls for broadly accepted standards for grades of atherosclerosis, normal and abnormal, as well as the pathological changes of coronary heart disease. The main consideration is an ability to differentiate during life the various forms or stages of the disease so defined, including inapparent manifestations. The promise of a practical precision is in development of laboratory measurements in aid of clinical examination, as for specific nutrients in dietary deficiency diseases or antibodies in infections.

An Epidemiological Approach. Appraisal of what has been accomplished in a developing knowledge of coronary heart disease suggests the need to bring into play to a greater extent than thus far done, that third general method for investigation of disease and injury: the study of a condition in its mass proportions, as it exists in nature, by epidemiologic techniques. The record of achievement of that method in communicable disease[218] and nutritional disorders[75] is distinguished; its practicability in modern problems of traumatic accidents[76a] and mental disorder[79,109] is confirmed.

Epidemiologic field method always has had its starting point in a command of clinical skills, the ability to recognize the disease under study in individuals of a population. For many years the laboratory has been an integral part of field investigation through realization that laboratory techniques are as essential there as in the clinic. The principle is firmly established, so definitely as to be practiced under the difficult conditions of the Arctic[11], and for degenerative[216] and other diseases as well as for the infections. With the problem of atherosclerotic coronary disease what it is and with the epidemiologic method so conceived, four of us have joined in this review of the community problem. Our common concern is the study of disease as expressed by Theobald Smith[185]; we have individual interests in internal medicine, experimental nutrition and epidemiology. The size and general nature of the community problem have first attention.

Statement of the Problem. Heart disease, all forms, superseded tuberculosis in 1912 as the leading cause of death in the United States, and has maintained that position consistently since then. The group includes coronary heart disease and excludes purely vascular disorders. The frequency of these conditions in relation to the general

population is necessarily judged by deaths; such facts as exist about morbidity, the more desirable criterion, are limited to a few sampling surveys on a local and occasionally a national basis. The relationship of deaths from heart disease to other chief causes of death for the last available year is shown in Table 1.

No more than an estimate can be made of the frequency of deaths from coronary heart disease, either in this country or any other. The bulk is listed in vital statistics under *Arteriosclerotic Heart Disease*, presumably something less than two-thirds[80,99,212a] being of that nature. Some cases are to be found under *Chronic Myocardial Degeneration*, with a few scattered under other headings. A figure of 150 deaths from coronary heart disease per 100,000 population per year in continental United States approaches reality but warrants no stronger rating than approximation. The rate alone exceeds that for cancer of all forms, the next general class. Compared with any one cancer or any other single disease, coronary heart disease is easily in the lead.

TABLE 1.—TEN LEADING CAUSES OF DEATH, CONTINENTAL UNITED STATES, 1954. DEATHS PER 100,000 POPULATION PER YEAR WITH CODE NUMBERS ACCORDING TO INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES, INJURIES, AND CAUSES OF DEATH, SIXTH REVISION, 1948.[221b]

Diseases of Heart (400–443)	348.3
Malignant Neoplasms (140–205)	145.6
Vascular Lesions of Central Nervous System (330–334)	104.1
Accidents (E800–E802, E810–E835, E840–E962)	55.9
Certain Diseases of Early Infancy (760–776)	39.4
Influenza and Pneumonia (480–483, 490–493)	25.4
General Arteriosclerosis (450)	18.8
Diabetes Mellitus (260)	15.6
Congenital Malformations (750–759)	12.5
Chronic Nephritis and Other Renal Sclerosis (592–594)	10.6

Source: U.S. Department of Health, Education and Welfare, Public Health Service, Washington (Publication No. 429).

TABLE 2.—HEART DISEASE, ALL FORMS, RATES PER 100,000 POPULATION PER YEAR, CONTINENTAL UNITED STATES, 1954, WITH CODE NUMBERS[221b]

All Diseases of Heart (400–443)	348.3
Arteriosclerotic Heart Disease (420)	235.6
Hypertension with Heart Disease (440–443)	46.6
Nonrheumatic Chronic Endocarditis and other Myocardial Degeneration (421, 422)	41.0
Rheumatic Heart Disease and Rheumatic Fever (400, 416)	12.1
Other Forms of Heart Disease (430–434)	13.0

Source: U.S. Department of Health, Education and Welfare, Public Health Service, Washington (Publication No. 429).

Heart disease as a class includes a number of disease processes, with arteriosclerotic heart disease outnumbering all others in the United States. Table 2 distinguishes the several entities recognized by the National Office of Vital Statistics[143] and in turn the World Health Organization[221b]. The category *Arteriosclerotic Heart Disease* accounts for about two-thirds of deaths from heart disease, with a crude rate of 235.6 deaths per 100,000 population per year.

The difficulties are magnified in an attempt to determine the trend of

deaths from coronary heart disease over the years. The quality of medical practice has changed, diagnostic criteria are different, and so are fashions in classification. How many deaths from acute myocardial infarction were entered on death certificates of other years as due to acute abdominal conditions or other noncardiac disease, will never be known; the number now is reasonably small.

Classifications of disease have been revised repeatedly, with the result that the same disease appears now here and now there. Before *Arteriosclerotic Heart Disease* appeared in the 1948 International List of Causes of Death, most coronary deaths were listed under *Chronic Myocarditis* although *Diseases of the Coronary Arteries* had been introduced in 1930. Before that, the rubric *Organic Diseases of the Heart* accounted for most deaths attributable to coronary heart disease. As revolutionary a practice as any came in 1948 when not the statistician but the physician became the arbiter of what was the principal cause of death.

Decision as to whether the increase in deaths from coronary heart disease

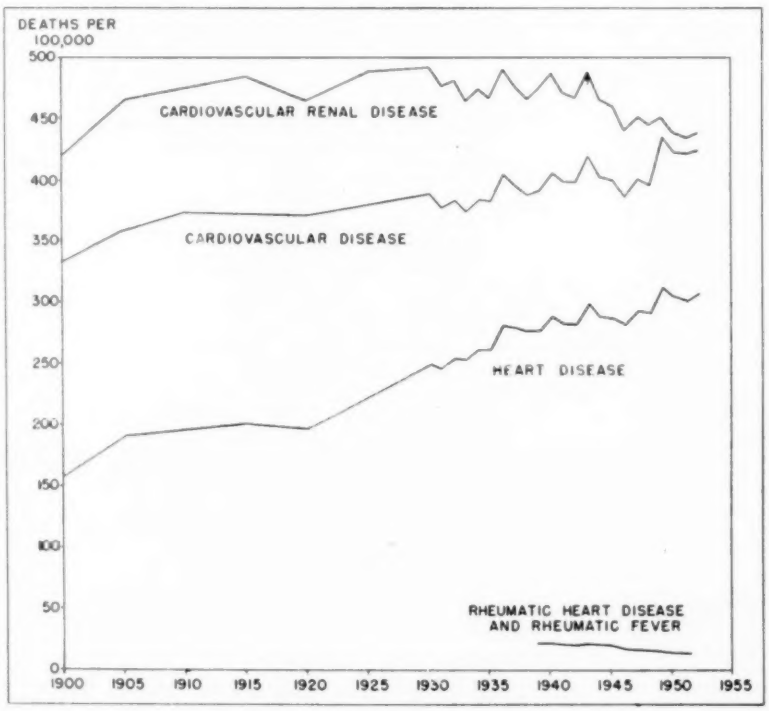


Fig. 3.—Age-adjusted death rates for specified major cardiovascular-renal diseases, deaths per 100,000 population per year, continental United States, 1900–1952. *Notes:* Heart disease category does not include rheumatic fever; comparable data for rheumatic fever are not available before 1939; change in method of assigning cause of death may account for all of apparent increase between 1948 and 1949. *Source:* American Heart Association[5]; Anderson, R. J., and Zukel, W. J.[6]; United States Public Health Service[205].

is real or related to factors such as those noted depends largely on indirect evidence. The only ready comparison is through consideration of heart disease as a whole, using age-adjusted death rates.

The population of the United States has been aging for a long time. The number of older persons is greater, and older persons have the greater risk of death from coronary heart disease. chiefly to coronary heart disease; that men were dying of coronary heart disease with equal frequency fifty years ago, but that death was mistakenly attributed to other causes is unlikely; no other cause of death with which coronary heart disease might be confused has shown a commensurate decrease[168].

The experience of older clinicians[149], cardiologists and general practitioners alike, yields the considered opinion that

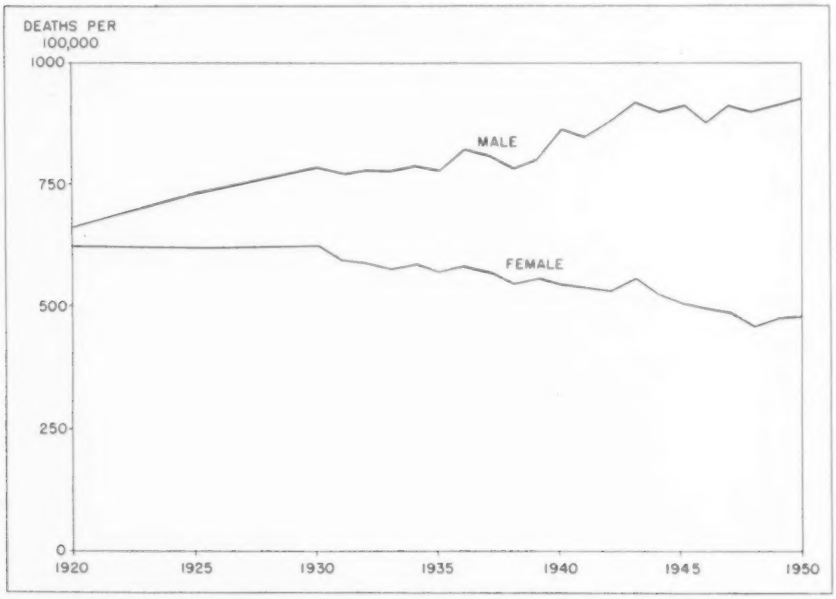


Fig. 4.—Cardiovascular-renal diseases, deaths per 100,000 population per year for persons aged 45 to 64 years, by sex, United States, 1920 to 1950. *Source:* American Heart Association[5].

With correction for age, death rates for all forms of heart disease have climbed steadily since 1900 (Fig. 3), more definitely than for the more inclusive classes of cardiovascular-renal diseases or cardiovascular disease.

That the trend for deaths of females aged more than 45 years from cardiovascular-renal disease is downward while that for males is upward (Fig. 4) has much meaning. The rise in deaths among males is attributable coronary heart disease is becoming more common, particularly at younger ages. A series of 3,000 cardiac patients was collected in 1925 by White[212a] from his own experience and that of colleagues. Comparison was made with a second series of 3,000 assembled in 1950. The proportion of cases identified as coronary heart disease was 20% in 1925; twenty-five years later it was 48.5%.

Necropsy material collected at the

London Hospital before 1914 was re-examined by Morris[137]. Sir James Mackenzie was then cardiologist, and Turnbull the pathologist had a special interest in atherosclerosis. Coronary atheroma were even more common then than now, but deaths from coronary heart disease were only one-seventh as frequent. A recent analysis of 7,032 general necropsy records from the Michael Reese Hospital, Chicago[170] demonstrates over the years an increasing proportion of deaths among older people. The material includes all deaths of patients aged 20 years or more for the period 1920 to 1953. Deaths from arteriosclerotic heart disease, however, progressively had stronger representation in the younger age groups. The summation of evidence speaks for an actual increased frequency of coronary heart disease in recent decades.

Pathogenesis. A working hypothesis of pathogenesis aids study of a disease in its mass proportions through indicating situations where data can be collected to advantage. Coronary heart disease is here postulated as a morbid process that results from excessive narrowing of the lumen or thrombus formation in atherosclerotic coronary arteries; further, that abnormal plasma lipid transport predisposes both to altered coagulability of the blood and to atheroma; and lastly, that disturbed lipid metabolism results variably from high intake of saturated fats, or relative deficiency of essential fatty acids, or from energy output (activity) insufficient for disposal of energy (caloric) intake including proper metabolism of muscle mass, or from long term neurohumoral reaction to stress. The initial lesion or plaque which is the basis for the later developments just described remains a fundamental enigma.

The Potential for Prevention. Assuming that coronary heart disease develops only in the presence of a pre-existing coronary atherosclerosis, ultimate control of the disease rests upon an understanding of the atherosclerotic process. However, a practical advance in prevention conceivably is possible through influencing favorably those factors which lead to excessive narrowing of the coronary arterial lumen and to thrombosis and infarction, with the assumption accepted that coronary artery disease remains essentially unchanged in frequency. These two premises guide examination of the epidemiological problem afforded by coronary heart disease.

Ecologic Analysis of Coronary Heart Disease. The simpler complex of an opposing host and environment serves necessarily in this ecologic analysis[76d] of coronary heart disease. No agent of the disease is known, if indeed one exists. The purpose is to assemble pertinent facts about coronary heart disease as derived from clinical, laboratory and field investigation, with separation into two broad categories; in the first instance, those which relate to the host and secondly, those concerned with the environment. Items pertaining to a particular characteristic within those categories are brought together and in turn related to pathogenesis and to recognized distributions of the disease within a population. The primary objective is a search for leads bearing on causation and behavior capable of further exploration.

Host Factors. Some host attributes relate primarily to the individual; others are group characteristics pertaining to populations and arising because of groupings of people. In both instances some are innate and some acquired, with genetic inheritance variously active.

Anatomical. Structural features of man clearly have to do with susceptibility and resistance to atherosclerotic

changes. Thickness of the coronary endothelium is generally accepted as greater at all ages in males than in females[43a,58,133]. Whether thickened intima predisposes to atherosclerosis or facilitates its development is not known. Mönckeberg[134] thought diffuse intimal thickening to be a normal event. In 626 specimens of aorta Wilens[214c] found a close association between diffuse intimal thickening and atherosclerosis, observing further that thickening does not occur in species failing in spontaneous atheroma. Herbivores have a thick intimal wall, notably elephants, but a general absence of atherosclerotic lesions[43b]. At least one instance is on record[117] however, of severe aortic and coronary arteriosclerosis in an elephant with death from coronary insufficiency. The intima of herbivores is highly vascular and that of man practically devoid of capillaries.

The vasa vasorum have had attention in pathogenesis of atherosclerosis and coronary thrombosis since Winternitz[219] observed them to be most numerous at the origins of branching arteries. The number generally increases with age, and they occur regularly in association with atherosclerotic lesions. Winternitz suggested subintimal hemorrhage from these vessels as a primary factor in lipid deposition and thrombus formation.

Atherosclerotic lesions of arteries tend to occur just distal to bifurcations[217a] and in regions of tortuosity[48]. For the coronaries that includes the proximal segments of the left anterior descending branch, the right coronary and the left circumflex branch, on the medial walls of the two branches and on the lesser curvatures[200]. The principles of hydrodynamics apply, as pointed out by Texon[200]. Such localization seemingly is favored by the stress of rapid blood flow, the strain from repeated changes in shape and the generally wider diameter just proximal to bifurcations[217b].

In a study of 86 radial and coronary arteries from necropsies of patients through a general age range, Sappington and Cook[171] described the fibroelastic transformation and thickening characeristic of aging[82] as maximal in the coronary arteries and minimal in the radial arteries, irrespective of coincident atherosclerosis.

Since Aschoff's[9] original observation, alteration in the ground substance of arteries has had much attention[29,57,136,199] but whether such changes are primary or secondary to lipid accumulation is unknown.

Blood. Despite the obvious relation of coagulation of the blood to coronary thrombosis, little study has been directed toward determining whether clotting in this disease is abnormal or a natural secondary event. Furthermore, Rokitansky's[164] early theory of the thrombotic pathogenesis of atherosclerosis and the role of coagulation largely was ignored until the work of Duguid[49a] who postulated recurrent fibrin deposition on the intimal surface as the initial lesion in atheroma. Experimentally, the fibrin was covered by new endothelial overgrowth, ultimately to degenerate with a resulting typical atheromatous lesion. In support of these observations examination of material from aortic lesions, judged by conventional methods to be collagen, was demonstrated by electron microscopy[115] to be fibrin. In postulating a temporary thrombotic state in thromboembolism, Wessler[211] emphasized increased coagulability of the blood as of greater significance than the traditional accent on intimal damage and stasis.

Subintimal hemorrhage from fragile, newly formed capillaries[159] also may contribute to growth of atheroma, to the extent of complete vascular occlusion.

Blood Pressure. A comprehensive clinical series[126] indicates a positive correlation for white women between cor-

onary heart disease and hypertension but not for men. The association in Negroes is rather definite; of 54 cases of myocardial infarction[210] 47 had hypertension.

The level of sphygmomanometric intra-arterial pressure indicative of the hypertensive state is always a question[35]. Lee and Thomas[114a] approached the problem by correlating kidney size at necropsy with acute myocardial infarction, on the assumption that long-standing hypertension commonly results in contracted kidneys. They conclude that "these data fail to provide definite support for the concept that hypertension is an etiological factor of importance in coronary arteriosclerosis in women." They did not, however, take into account what the blood pressure may have been during life. A recent report of 1,600 patients with coronary heart disease[194] gave 56% females hypertensive as against 31% of males; values of this order are the common finding.

The pulmonary vessels ordinarily are free from atherosclerosis[202], but the condition is common with increased pulmonary pressure, suggesting blood pressure as a factor in pathogenesis. The sluggish blood flow in hypotension presumably increases the chances of thrombus formation. An increased frequency of acute myocardial infarction is noted with surgical[113] and insulin[98] shock.

Most animal experiments[26,189a,214a] support the hypothesis that hypertension favors atherogenesis. The results of Wissler[220] discount increased blood pressure as the actual mechanism, and suggest a more obscure, perhaps a renal factor.

Hormonal Influences. The relative infrequency of coronary heart disease in women before age 50 years, and the increasing frequency thereafter, suggest protective action by ovarian hormones. The effect of estrogenic substances has been studied in patients and in experimental animals. Oöphorectomized women apparently develop appreciable coronary atherosclerosis at younger ages than normal women[222]; conversely women with the hyperestrogenism[161] usually associated with breast cancer have less coronary sclerosis.

Patients with prostatic carcinoma treated with estrogens seemingly had less coronary heart disease than expected[68]. Estrogens limit coronary but not aortic experimental atherosclerosis in hens[189b], an effect accompanied by increased serum cholesterol and more significantly, an increase in serum phospholipids.

The effect of androgens is less definite. The clinical impression that castrated men have less than usual frequency of coronary heart disease was supported by an unpublished study[13] of legally sterilized males. Neither testosterone nor castration had any particular effect on rats of either sex fed atherogenic diets, in respect to coronary atheroma or to serum lipids[142].

Thyroid hormone has a definite effect on blood lipids and less definitely on atherosclerosis. Severe myxedema[130] is associated commonly with hypercholesteremia and increased atherosclerosis. Dogs were believed resistant to experimental atherosclerosis until thyroidectomy[191], together with a dietary regimen similar to that used experimentally for rabbits, gave a successful result. No increase in arteriosclerosis was found on observation of thyroidectomized patients with coronary heart disease[21] 20 years or more after operation.

Adrenal cortical steroids alter the level of serum lipids, with the direction and magnitude of change dependent on dosage and kind of hormone[106]. An adrenal effect[2] on the rate or degree of development of atherosclerosis has not been clearly demonstrated. ACTH had

little effect[2] on lipid level of the cholesterol-fed rabbit, although thought to inhibit atherogenesis under these conditions. Continuing interest is exhibited in the action of the so-called pituitary-adrenal axis in situations of stress, and thus indirectly on coronary heart disease[178,188]. Indirect evidence comes from experiments in which rats were subjected to extreme cold[177] with presumably excess production of adrenal corticoid. Serum cholesterol was elevated and marked atherosclerosis of coronaries and aorta resulted after 18 months on an ordinary laboratory diet; after 6 weeks, with added cholesterol and fats.

Age. From knowledge of 7,941 elderly patients of whom 863 had remote or recent coronary occlusion, Monroe[135] observed that, "although coronary sclerosis seems to increase with years, the event of occlusion of a sclerotic artery seems not to be so associated, but rather to be precipitated by other factors." The challenging question is why do not more people develop coronary heart disease with aging; what is there about the people who do which sets them apart from those who do not?

In 536 necropsies of patients ranging in age from the newborn to 89 years, Lober[118] gained the impression that atherosclerosis progresses through life at a nearly uniform rate. Lesions were more pronounced among males than females, and among patients with concomitant hypertension and diabetes mellitus; they were less evident than usual in the presence of malignant neoplasm.

In respect to prognosis, a study of 865 patients with coronary heart disease from 1930 to 1950 led Peel[153] to conclude that the risk of death is less for men of 50 to 54 years than for those younger or older. In an effort to account for factors other than aging, Smart and Bruce[183] applied the *Pathologic Index Rating* (PIR) of Schnur[175a] to 160 patients with unequivocal myocardial infarction. This mathematical procedure is based on major factors believed to affect prognosis adversely. Older people tended toward higher PIR values, but with many discrepancies in the association. Fatality was lowest at ages 40 to 49 years, while the four patients aged 30 to 39 years all died in the acute attack.

Atherosclerotic changes seemingly are an earlier event than ordinarily believed. Pathologists commonly observe fatty streaking on the surface of aortas of infants, but some[148] have the impression that these early lesions, scarcely to be called atherosclerosis, regress after weaning. Coronary heart disease is rarely observed in infants; Leach[111] recently reported a 9-month-old boy without other discernible disease who died in congestive heart failure due to acute myocardial infarction. The observation[54] that 77% of 300 necropsied United States battle casualties in Korea, mostly in their early twenties, had "gross evidence of coronary disease" is frequently cited as demonstration that most young Americans suffer from coronary artery disease. About one-half of those affected had fibrous thickening of the intima, about one-half also had varying degrees of arterial narrowing. Nine had complete occlusion of one or more coronary vessels. No one was known to have had symptoms suggestive of coronary heart disease.

The dominant influence of increasing age on frequency of coronary heart disease is illustrated for the United States population in Fig. 5 by data on arteriosclerotic heart disease, of which about two-thirds is coronary heart disease. Age is a factor for both whites and nonwhites and for both sexes. These distributions are usual in countries where coronary heart disease is a problem.

Sex. Males exceed females among patients with coronary heart disease aged less than 45 years in a proportion variously estimated[173,209] at from 2:1 to 7:1 or more. One hundred young coronary patients of Gertler and White[70] included only 3 women. Among 95,000 women patients at the Mayo Clinic[204], only 27 had coronary heart disease, of whom 17 were hypertensive. Of 617 cases of sudden coronary death[158], only 6% involved women.

The differences are less with increasing age[20]. A recent review of 8,183 adult necropsies[114b] over a period of 45 years included 500 cases of myocardial infarction, with an over-all sex ratio of 1.2:1, a significant difference. The important consideration is that a ratio of 2:1 in former years had changed to give an approach to parity.

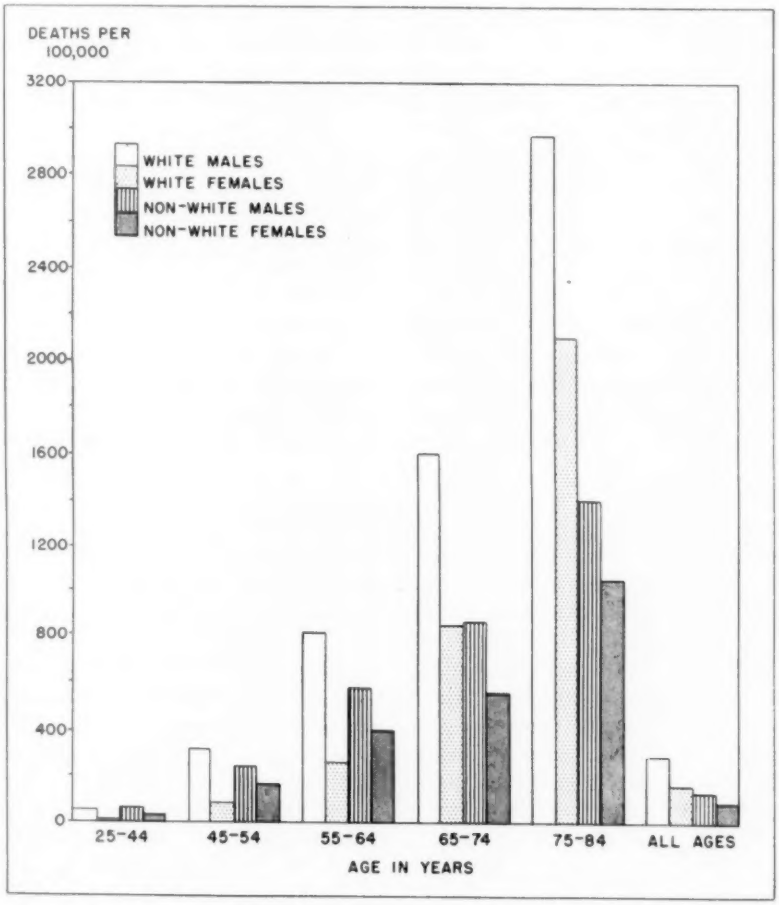


Fig. 5.—Death rates per 100,000 population per year for arteriosclerotic heart disease, including coronary disease, by age, race and sex, continental United States, 1950. *Source:* United States Public Health Service[205].

The lesser frequency of coronary heart disease in women than men should not lead to the generalization

that atherosclerosis also is regularly less. Survey of an industrial population of 32,000 by Boas and Epstein[23], for coronary, aortic, cerebral and peripheral arteriosclerosis gave frequencies of aortic and cerebral lesions for women practically the same as for men. Coronary and peripheral arteriosclerosis predominated in men. The effect of estrogens in inhibiting experimental coronary but not aortic atherosclerosis[189b] supports this clinical observation.

Demographic data for arteriosclerotic heart disease in the United States, Fig. 5, demonstrate a regular excess of deaths among men at all ages. The differences between men and women, especially white persons, are more pronounced at younger ages, with the gap tending to close at ages past 75 years. The sex relationship holds for nonwhite as well as white fractions of the population, although less pronounced among Negroes and other nonwhites.

Race. Racial differences in frequency of coronary heart disease have been surmised but never demonstrated. The crude mortality rates for cardiovascular disease in the United States in 1950 were 512 deaths per 100,000 per year for whites and 498 for nonwhites. Arteriosclerotic heart disease accounted for about 23% of all nonwhite deaths; the comparable figure for whites was 44%. The data make no allowance for population differences in age and no means are at hand to assess such factors as quality of medical care and accuracy of medical certification.

An Air Force hospital in Alabama[101] admitted patients in the general proportion of 70% Negro and 30% white. Of 519 cases of proven myocardial infarction, Negroes contributed only 79% of expected numbers and whites 150%. The number of Negro women was essentially that of Negro men while the ratio of white women to white men was about 1:3. Accumulating evidence suggests these differences as mainly due to environment, particularly the social environment, race being a lesser consideration.

In an American industrial population[55], the frequency of manifest atherosclerosis was greater among Jewish than Italian workers. Extreme differences exist in the frequency of atherosclerosis and of coronary heart disease from one country to another[221a].

Species differences are strongly evident for both conditions. Only man and birds commonly develop spontaneous atherosclerosis, sometimes old rabbits and rats[129]. All other species have a natural resistance on the natural diet, a fact to be considered in interpreting experimental disease.

Genetic Factors. Efforts to demonstrate a genetic inheritance of coronary heart disease in man are unconvincing, except secondarily through such diseases as diabetes and familial hypercholesteremia[1]. A family history of much cardiovascular disease was more frequent among patients of Gertler and White[70] and of others[201] than in the general population. The matter warrants exploration by modern genetic methods, with consideration of occupation and other factors of the social environment. No direct studies on the relation of blood groups to coronary heart disease are known.

Body build is to a large extent congenitally determined[179]; obesity is probably determined more by environmental than constitutional factors[128]. Those concerned with life insurance data[180] have noted that obese persons have a shortened life expectancy, with coronary heart disease one of the reasons. Despite the selected nature of the sample, the results are provocative. Clinical and necropsy studies have for the most part borne out this association[37,127] but discordant findings exist.

Of 240 patients with acute myocar-

dial infarction[18] those judged obese had an immediate fatality of 32%, those of average weight 39%, while the rate for underweight patients was 60%. The fatality for obese patients of both sexes (16%) was less than the over-all fatality (24%) of a group of 920 patients with coronary heart disease reported by Smith *et al.*[154]. Yater[223] found the same proportion of overweight individuals among 866 young patients with coronary infarction in the Armed Forces as in a control group of 297 soldiers killed accidentally.

Weight reduction is claimed to improve prognosis of obese patients with coronary heart disease[74,140,214b]. The question is unsettled. The preferred technique of fixed sample is not usual, nor is bias from other influences eliminated. It is not certain that the reported result is from simple loss of pounds or from the kinds of diet which bring it about.

The apparent relation of body build to chance of developing coronary disease is impressive. That coronary thrombosis occurs most frequently in mesomorphs and rarely in ectomorphs was an early observation[156]. The careful study by Spain[187] of 73 young men dying an accidental death and 38 who died of coronary heart disease demonstrated a greater degree of atherosclerosis in those preponderantly mesomorphic, but little correlation with obesity. The same association with mesomorphy was evident in Gertler and White's[70] group of young patients with coronary heart disease. Granting somatotyping to be a valid measurement, the main question is the feature of mesomorphy directly responsible. It seems not to be excessive androgen.

Psychic Constitution. The concept of an inherited coronary personality[14] has been advanced but scientific support is nonexistent. This does not discount what every physician and most people know, that the personality pattern of a person, representing both inherent and acquired attributes, has much to do in determining the reaction to environmental stress. Presumably, unknown or unevaluated features of the psychic makeup of man will one day prove useful in prevention of coronary disease. Any penetrating study into causation reasonably gives attention to clues in this direction, through thoughtful observations carefully recorded.

Synergism and Antagonism in Coronary Heart Disease. That one disease may change the course of another[198] is an old, a familiar, and a poorly understood observation. The effect in nature is sometimes protective and sometimes detrimental. The choice as to unit of observation is either the single patient and the method of study clinical, or a population of people with disease in mass proportions examined epidemiologically.

Patients with diabetes mellitus have long been known to suffer more severe atherosclerosis and at an earlier age than nondiabetics. Since insulin, severe hypercholesteremia is a less common complication but whether or not arterial degenerative changes have been reduced is another question. Specialists in diabetes such as Joslin[98] and Dunlop[50] believe that good control results in less atherosclerosis. Another series of 383 randomly chosen diabetics of all ages[116] demonstrated an association between arteriosclerotic heart disease and older age, for the male sex and the presence of hypertension. There was no correlation with obesity, cholesterol level or degree of control or duration of disease. In a review of the problem Dolger[44] concludes that "present day treatment of diabetes has failed to avert the accelerated vascular damage, which is an associated phenomenon of the disease and not a complication."

Cook *et al.*[38] described alloxan dia-

betes as inhibiting atherosclerosis in the cholesterol-fed rabbit. This protective effect was accompanied by significant changes in the lipid pattern, a decrease in the cholesterol-phospholipid ratio.

Most diseases commonly associated with atherosclerosis and coronary heart disease are characterized by high levels of serum cholesterol and other lipids. Familial xanthomatosis is the classic example, where coronary heart disease is commonly manifest at an earlier age, and blood lipid levels are much higher than usual. Serum cholesterol levels are characteristically high in patients with myxedema and nephrosis, and coronary heart disease is known to occur at early ages[61] in nephrosis, but a greater frequency is not certain for either disease.

Hypercholesteremia is frequent in chronic gallbladder disease but with no tendency toward an excess frequency of atherosclerosis or coronary disease even in women after the menopause. Coronary occlusion occurred in 20% of 165 cases of cholesterosis of the gallbladder[59]; among 1,319 controls the frequency was 22.6%. The hyperlipemia of chronic biliary cirrhosis is, however, characterized by a low cholesterol-phospholipid ratio[99].

Inflammatory endarteritis and myocarditis conceivably have the capacity to predispose through vascular trauma to localized atheroma. Of some 10,000 patients with cardiovascular disease, 2,800 had coronary heart disease, another 1,346 had rheumatic heart disease. Only 32 patients had both. Gardner and White[66] concluded that rheumatic heart disease does not predispose to coronary heart disease.

Environmental Influences. Environmental factors bearing on the origin and frequency of coronary heart disease are separated to advantage into three categories, the physical, the biologic and the social environment; ecologic analysis is according to an established pattern[77,79]. The physical environment has to do with such things as climate, altitude, radiant energy and toxic chemicals.

Physical Environment. In most localities of temperate zones, the greatest frequency of coronary deaths is in winter[15,213]. Seasonal stress in warmer areas is greater in summer than winter, with suggestion of a reversed frequency. Data from Dallas, Texas[92], support that view but recent information from Houston of the same state[175b], demonstrates the usual winter frequency. Both Petersen[155] and Mills[132] have provided fascinating speculation on meteorologic influences on arteriosclerosis and hypertension but weather data are complicated and there are no data helpful to an understanding of coronary heart disease.

Ultraviolet light[4] is reported to have induced a significant decrease in serum cholesterol levels for 61 of 78 hospital patients with a variety of diseases. Radiant energy seems to have an inhibiting effect on experimental atherogenesis[91], possibly through lowered serum lipid levels. A relation to coronary heart disease has not been tested.

Carbon monoxide is probably the most common toxic fume. A suggested causal relation to heart disease[16], not specifically coronary heart disease, is taken care of nicely by Donald Hunter[96] who denies the existence of chronic carbon monoxide poisoning and states the only ill effect of the acute condition on the cardiovascular system is aggravation of existing disorders in old people and cardiac patients.

A variety of chemical compounds of high molecular weight, such as methyl cellulose, polyvinyl alcohol and gum arabic, injected into animals susceptible to atherosclerosis, produce intimal lesions similar to those associated with hypercholesteremia. Hueper suggests

that these agents have the common effect of producing intimal anoxia, and that this is the precursor of atherosclerosis[95a,b].

The biologic and pathologic effects of tobacco smoke have been documented[166], but a clear-cut effect in causation of coronary disease has not been demonstrated. Electrocardiographic and ballistocardiographic changes are commonly seen after smoking[81,87], and anginal symptoms, presumably due to decreased coronary flow, are described after cigarette smoking[141,165]. Epidemiologic interests have turned recently to a variety of diseases and their frequency among smokers and non-smokers. In the United States[86] death rates for coronary heart disease were twice as high for smokers of one to two packs of cigarettes daily as for non-smokers. In British experience[45] on the other hand, the small increase in deaths from coronary heart disease was insignificant compared with that for cancer of the lung. A general review by McDevitt and Wright[129] produced no evidence that tobacco is an etiologic factor in coronary heart disease, but that once established its use has an adverse effect. Heavy use of tobacco and coronary heart disease may be no more than coincidental in persons prone to atherosclerosis.

Biologic Environment. Infectious agents and diet are the important features of the biologic environment in relation to coronary heart disease. Because nutrition governs lipid metabolism, that subject is included.

INFECTION. Evidence of a specific infectious agent of coronary disease is wholly lacking. It is possible that vascular reactions to certain microbial agents may predispose to the disease[169]; cholesterol-induced atherosclerosis in the chick is believed enhanced by intestinal infection[152]. Modern control measures for communicable disease have so reduced incidence that many more people now live to develop coronary heart disease. The relationship seems little more than that, an opportunity for aging and atherosclerosis. When infections in childhood were commoner, coronary heart disease was at an older age than now; with fewer infections the age of attack is earlier and the disease more frequent.

NUTRITION. The metabolism of selected nutrients has a part in the genesis of both atherosclerosis and the thrombosis which underlie coronary heart disease. Since the discovery by Vogel[206] that human atheromatous lesions are rich in cholesterol, and of Anitschkow[8] that cholesterol-fed rabbits develop aortic atheroma, abnormal lipid metabolism has dominated thought on pathogenesis. All methods for inducing atherosclerosis in animals produced that result through increased serum cholesterol concentration, the single exception being the choline-deficient rat. Patients with coronary heart disease average a higher level of cholesterol than do controls[147c,190]. However, values vary widely with age[103,147a] and social status, and average differences are not always distinctive.

Ingested fat and cholesterol pass the intestinal lymphatics mainly as insoluble chylomicra[30]. Patients with coronary heart disease have elevated chylomicron counts for long periods after a meal but individual variation and laboratory error make the test impractical[65,144]. Cholesterol is synthesized in the liver. It is esterified with fatty acid and phospholipid, and combined with protein to become soluble in blood[62,196]; endogenous cholesterol level apparently varies inversely with the amount of ingested cholesterol[197]. Cholesterol feeding has led to hypercholesteremia and atherosclerosis in the

rabbit[112b], guinea pig[39], fowl[40] and more recently in the monkey and rat[7]. A consistent hypercholesteremia does not follow ingestion of cholesterol by man[60].

Other fats have a marked effect on serum lipids in man. Saturated fatty acids lead to hypercholesteremia while certain unsaturated ones markedly lower blood cholesterol, a fact recently demonstrated[3], and repeatedly confirmed[17,88,107]. The degree of unsaturation appears more important than animal or vegetable origin; after hydrogenation vegetable oils no longer exert a hypercholesteremic effect[25]. The mechanism is unknown, but Sinclair[182] has theorized that cholesterol esterification with nonessential, saturated fatty acids results in esters which are poorly metabolized and thus accumulate in the plasma. He suggests that essential fatty acid deficiency is a cause of coronary heart disease.

An improved understanding of lipoprotein metabolism has contributed to the role of lipids in atherogenesis. All plasma lipids are now known to be combined chemically with alpha and beta globulins of the plasma protein. By chemical fractionation[167], or by electrophoresis[108] two main groups are distinguished. Alpha lipoproteins are small, dense molecules with little cholesterol in relation to phospholipid; beta lipoproteins are larger, less dense and richer in cholesterol[195]. A high concentration of beta lipoprotein is frequently associated with coronary heart disease and other atherosclerotic disease, both in humans and in experimental animals[51]. Equally good correlation exists between atherosclerotic disease and a high ratio of cholesterol to phospholipid[69]. Low cholesterol-phospholipid ratios appear to increase the solubility of blood lipids and to protect against coronary atherosclerosis. Normal women have lower cholesterol-phospholipid ratios and higher a/b lipoprotein ratios than men; males treated with estrogens manifest the female lipid pattern[147b].

Further knowledge of lipid metabolism in health and disease has come from the ultracentrifugal flotation technique of Gofman *et al.*[73]. Beta lipoproteins apparently exist in series progressing from Sf_0, the smallest and most dense, up to $Sf_{20,000}$, which are chylomicra[72]. Gofman believes that in normal persons few lipoproteins above Sf_6 are present in plasma except during alimentary lipemia, when a transient rise and fall occur in the larger, lighter macro-molecules. In atherogenic conditions a metabolic block presumably interferes with the normal serial degradation of higher lipoproteins down to the Sf_{0-6} classes. In coronary heart disease, and in other conditions characterized by atherosclerosis, high concentrations of Sf_{12} to Sf_{∞} are usual. The test is suggested as of diagnostic value in subclinical coronary disease. In an effort to develop a test which would check with actuarial data on coronary heart disease, Gofman *et al.* devised a mathematical formula, based on age, as well as lipoprotein values, to compute an accumulated coronary disease (ACD) value[72,119]. This was done because of the failure of lipoprotein alone to provide an accurate measure. Some[33,46,151] still doubt that it has been done.

Disagreement on the merits of Sf lipoprotein and cholesterol measurements in detection of atherosclerotic coronary disease has influenced the National Advisory Heart Council[159] to undertake cooperative studies of serum lipid determinations in health and disease at four centers, Berkeley, Cleveland, Boston and Pittsburgh. The estimation of total cholesterol is much simpler, which raises the question of whether or not it is necessary to employ the more complicated test by ultracentrifuge.

The observation by Hahn[84] in 1943

that lipemic serum clears after intravenous administration of heparin, led to a new concept in pathogenesis of coronary heart disease and the possibility of a preventive measure. The decreased turbidity of lipemic serum *in vivo* after administration of heparin is due to a lipoprotein lipase activated by heparin and enzymatically hydrolizing higher Sf lipoproteins to form smaller lipoprotein molecules and free fatty acids[28,162]. Patients with coronary heart disease exhibit impaired clearing of lipemia after intravenous heparin[19,99]. Whether or not endogenous heparin functions physiologically in fat transport is unknown, but the possibility that heparin deficiency may be important in coronary heart disease has suggested its use in prophylaxis. Heparin and other anticoagulants have been used extensively in acute myocardial infarction to limit thrombosis, but the small dosage sufficient for clearing effect does not prolong clotting time. Since clotting *in vitro* is shortened by lipemia[63,207], lipemia clearing may also inhibit intravascular coagulation[146].

Therapeutic trial of heparin in angina pectoris has given conflicting results[32,83]. However, only 4 deaths from cardiovascular disease occurred among 105 patients[53] recovered from myocardial infarction and subsequently treated with bi-weekly heparin injections, compared with 21 such deaths among 117 controls judged to have had equally severe disease and carried on a comparable schedule of saline injections. The probability of such a difference occurring by chance is less than one in a hundred. That Dicumarol as well as heparin minimizes atheroma formation in cholesterol-fed chicks[94] suggests the anticoagulant effect to be the more important, and also supports Duguid's[49b] emphasis on the thrombotic pathogenesis of coronary atherosclerosis. Much more study of this debated preventive measure is essential to final conclusions.

Aside from the question of whether lipids are primarily or secondarily concerned in atherogenesis, the mechanism by which they are deposited in vascular lesions is important. Simple filtration enhanced by intravascular pressure and fatty degeneration of mural thrombi are explanations. Other theories have been suggested but with no convincing proof. Phagocytosis by foam cells as advanced by Leary[112a] and intravascular synthesis of cholesterol[34] both occur, but probably in insufficient degree to account for sizable lesions. Using tissue culture techniques Simms[181] has described lipfanogens, occult substances of unknown nature converted by endothelial cells into visible fat.

Nutrients other than lipids acting variously through excess or deficiency, are known to have a part in atherogenesis, although probably secondary in nature through facilitating more evident causative factors. Diets high in protein and low in fat plus added salt produce typical aortic atherosclerotic lesions in rabbits[145] suggesting the importance of a renal or adrenal factor. Choline deficiency, both acute and chronic, causes coronary and aortic atheromata in rats[215] without the usual elevation of serum cholesterol, and atypical also in the severe fatty degeneration of liver and kidney.

A deficiency of sulfur amino acids, mainly methionine, along with added dietary fat and cholesterol produces coronary atherosclerosis in the cebus monkey[122] an animal otherwise resistant. Lesions were absent when the diet had no choline, suggesting that deficiency of lipotropic factors was not the mechanism. Atherosclerosis, including coronary atherosclerosis, has been produced in the rhesus monkey by a diet deficient in pyridoxine[160]. As a causative factor in coronary heart dis-

ease Schroeder[176] gives more weight to pyridoxine deficiency than lipid disturbances.

An important consideration in all experimental atherosclerosis is that atherosclerotic lesions of the coronary arteries are rarely associated with thrombosis.

ent countries, Table 3, are so distinct as to direct a main attention to social forces, among others the provision for medical care. Existing evidence on peculiarities of race, geography or climate scarcely accounts for such variations. Without exception, countries of high economic development have the

TABLE 3.—DEATHS FROM ARTERIOSCLEROTIC AND DEGENERATIVE HEART DISEASE, CODE NUMBER 420–422,[221b] AND OTHER DISEASES OF HEART, CODE NUMBERS 400, 416, 430–434, 440–443[221b] PER POPULATION PER YEAR, FOR SELECTED COUNTRIES AND YEARS, 1951 TO 1954.

		Arteriosclerotic and Degenerative Heart Disease		*Other Diseases of Heart*	
Region	*Country*	*Number*	*Rate*	*Number*	*Rate*
North America	United States (1953)	446,927	282.3	22,612	14.3
	Canada (1954)	33,810	222.9	1,860	12.3
	Mexico (1952)	1,490	5.5	18,017	66.0
South America	Chile (1953)	2,294	36.2	5,755	90.8
North-West Europe	England and Wales (1953)	131,436	298.0	7,530	17.1
	Sweden (1953)	16,457	229.5	2,527	35.2
	West Germany (1953)	79,988	163.3	11,856	24.2
	Netherlands (1953)	15,453	147.3	1,930	18.4
	Norway (1953)	4,546	135.3	1,080	32.1
	Belgium (1953)	9,817	111.8	12,407	141.3
Mediterranean	Italy (1953)	83,658	176.3	6,469	13.6
	Yugoslavia (1953)	4,658	124.6	701	18.8
	Israel (Jewish Population) (1954)	1,814	120.9	206	13.7
	Egypt (1952)	2,524	28.2	1,216	13.6
Africa	Union of South Africa (1951)	4,330	163.4	390	14.7
Far East	Japan (1953)	38,718	44.7	14,119	16.3
	Ceylon (1954)	2,097	25.0	1,213	14.5
	Taiwan (1953)	308	3.7	2,546	30.8
Australasia	New Zealand (Exc. Maoris) (1953)	4,850	252.2	528	27.5
	Australia (1953)	21,237	240.9	2,110	23.9

Source: Demographic Year Book 1955, New York, United Nations, 1956.

Social Environment. As a social animal, man is decisively influenced in his behavior by the customs, attitudes and beliefs of those with whom he lives, and also by social, economic and political organizations within that society. To a great extent dietary habits are socially conditioned and so are occupation, physical activity and reaction to stressful situations.

Differences in recorded deaths from arteriosclerotic heart disease in different countries, Table 3, are so distinct as to direct a main attention to social forces, among others the provision for medical care. Existing evidence on peculiarities of race, geography or climate scarcely accounts for such variations. Without exception, countries of high economic development have the higher mortality. The low rate for Belgium is seemingly artificial; that for *Other Diseases of the Heart* is correspondingly high.

Food Economics. During World War I[93] death rates from cardiovascular diseases fell off in areas where food supply was restricted, an experience repeated during World War II[42,121,193]. The lesser rates, which hold also for general thromboembolic phenomena as well as for coronary heart disease, rose

to pre-war levels when wartime conditions ended. Observers[102] attribute the effect to low intake of dietary fat, with the psychologic and physical hardships of war unimportant or even operating beneficially in regard to coronary heart disease. However, it is well to point out that diets low in fat usually vary in other nutritional characteristics from high fat diets. Thus they are usually high in fiber and starch and low in protein and vitamins. There may also be a change in intestinal flora, so that nutrients other than fat must be considered in low fat diets. If changes in diet were responsible, the mechanism may be equally well an altered coagulability of the blood or a regression of atherosclerosis.

A relation between dietary fat, serum cholesterol concentration and prevalence of coronary heart disease has been explored geographically by Keys *et al.*[27,104,105]. In Naples, Sardinia and Madrid, mortality for arteriosclerotic heart disease is relatively low. However, groups of low income workers in apparent health had lower serum cholesterol levels and lesser fat intake than more affluent citizens. The latter had an appreciable frequency of coronary heart disease; hospital records revealed few cases among ward patients. The results are only suggestive because of the short term observation, difficulty in estimating dietary intake, especially fats, and none too certain data on coronary heart disease.

Much the same situation has been noted in Puerto Rico where Amadeo[4a] found far less coronary heart disease among natives living in the interior of the island where a deficient diet resulted in chronic anemia than in the City of San Juan where the diet was better and anemia infrequent.

The prevalence of coronary heart disease in the same racial stock but living in different environments is a pattern of field investigation directed toward differentiating constitutional and dietary factors in coronary heart disease. Preliminary results indicate that Japanese in Hawaii[110] with a diet richer in fat have serum cholesterol at higher levels and that coronary heart disease is more common and at younger ages compared with Japanese in Japan[212c]. Similarly, South Italians living in Boston had significantly higher serum cholesterol and fat intake than Italians in Naples[203]; the influence of other social factors and a relation to coronary heart disease in these two Italian groups have not yet been evaluated.

Physical Activity. The adverse effect of excess physical activity on angina pectoris and during the healing stage of myocardial infarction is recognized. A relationship between such activity, occupational or otherwise, and onset of coronary thrombosis or atherogenesis is indefinite. Indirect evidence relating physical inactivity as a factor favoring coronary heart disease comes from recent laboratory, clinical and population studies.

Heart muscle, according to Raab[157], contains the sympathetic amines epinephrin and norepinephrin in unusual concentration. Norepinephrin promotes efficient oxygen utilization and predominates in the myocardium of trained athletes. Epinephrin, an oxygen-wasting substance, is higher in hearts of sedentary persons, especially those with coronary heart disease. On the assumption of poor myocardial response to diminished blood flow being a more important factor than narrowed coronary arteries, he generalizes that physical inactivity, so common to our civilization, is a major cause of coronary heart disease.

Healthy men on diets that produced obesity and hyperlipemia under conditions of normal activity, by increased

physical exercise were able to maintain normal weight and prevent hyperlipemia[125]. The disposal of caloric intake by energy expenditure rather than by accumulation of fat was believed more decisive in regulating serum lipid than the amount or kind of food ingested. Native Guatemalan and Nigerian peasants[123,124] have little coronary heart disease, low serum cholesterol levels, but beta lipoprotein values that approximate those in the United States. The natural physical activity of these primitive people as well as the low fat, low protein diet they characteristically consume was interpreted as providing protection from coronary heart disease.

From mortality data of England and Wales, Morris[138,139] concludes that deaths from coronary heart disease are significantly less for heavy laborers than for professional workers. To separate the effect of physical activity from social class, he determined the frequency of coronary heart disease among London transport workers. Conductors, whose activity on double-decker buses is considerable, suffered more angina but less infarction than did the sedentary drivers. Such studies warrant elaboration to determine other potential influences, along with serial observations necessary for a definitive answer on how much coronary heart disease.

Emotional Stress. Since John Hunter's prophetic assertion that his life was at the mercy of any rascal who provoked his temper, the view is common that anger, fear and anxiety precipitate coronary heart disease in susceptible individuals. Scattered investigations[10,208] give inadequate support to this unestablished hypothesis. Cannon's[31] classical studies on homeostasis included information that cats experiencing fear and rage had a markedly shortened clotting time, by way of sympathetic stimulation of the adrenal medulla, a confirmed result[174]. Intravascular coagulation is a key factor in coronary thrombosis.

Selective stimulation by discrete hypothalamic centers of cells of the adrenal medulla secreting epinephrin and norephinephrin has recently been shown experimentally[56]. Psychophysiologic studies in man suggest that situations which cause anxiety produce marked secretion of epinephrin rather than norepinephrin[64].

There may be general agreement that emotionally charged situations are bad for the patient with coronary heart disease but it has never been shown[131] that the emotional reactions of such patients differ significantly from those of the general population.

Application of Epidemiolgical Method to Coronary Heart Disease. Most medical activities with a part in the prevention and control of coronary heart disease have recognized the challenge for epidemiological research. Official health agencies[97] find field investigation a necessary feature of programs for control of heart disease; laboratory investigators[100,124] incorporate field method as an adjunct to biochemical procedure; some of the stronger supporters are among clinicians[24,212b]; and epidemiologists have initiated studies in this[41] and other[137] countries. A growing regard for the usefulness of the epidemiologic method in heart disease is a feature of the past 10 years. This is evident in current editorial comment[52a,b] by medical journals and a firm backing by organizations responsible for research[47].

An inventory of materials available for study, of sources of existing information and elective procedure in epidemiologic method has the aim of revealing opportunity for field studies. In the beginning it is purposeful to recognize that epidemiology is a disci-

pline having its own body of knowledge and its own particular uses, but that primarily it is a method of study applicable to medical investigation generally.

The fundamental business of epidemiology is to define the pattern of behavior of a disease in communities of people, in this instance coronary heart disease. Incidence is determined for subgroups having different characteristics, and living under different environmental conditions[71]. The ecologic analysis just preceding has demonstrated uneven distributions between men and women, old and young, white and Negro, malnourished and overnourished, an industrial as contrasted to an agricultural civilization, and between the active and inactive. An established principle recognizes diseases with material differences in attack rates among divisions of a population as particularly suited to epidemiologic study. Some of these associations have more strength than others; few have been established at a cause and effect level. Meaning is enhanced by identifying a particular association in a number of subgroups, such as social status, rural and urban residence and occupation, with further test for internal consistency by making new population divisions.

A principal deficiency is that knowledge of the impact on populations concerns only a part of the process. The frequency distributions of coronary atherosclerosis are unknown. They may or may not correspond to those of the end process. Also in mass disease generally, the search for causes is favored by study of early forms, a feature having weight in this instance because both host and environment are much changed by the regimen imposed in management of the manifest disease. The relationships of coronary heart disease itself are ill-defined; death rates are little more than good estimates; morbidity has an even less secure foundation. In most instances available information is from populations of patients, which always carry limitations not a part of a general population. Much remains to be done about what was termed the fundamental business of epidemiology. With these reservations, profitable leads exist in a search for cause, which is the second larger purpose of epidemiological investigation.

With added pertinent knowledge from clinical sources, animal experiment and a variety of laboratory sciences, hypotheses are developed to test such associations for validity, consistency, and a causal relation. The particular problem determines whether that be by epidemiologic analysis, clinical investigation or laboratory experiment. When it is epidemiological, the question of populations by the nature of things is the first consideration; no people, no epidemiology.

Populations. The choice of a study population is within two broad classes: a general population which includes the sick and the well, and a population of patients with the disease. Each has the distinction of being open or closed. The closed population starts as a fixed unit and so continues with calculated allowance for attrition. The open population is subject to continued addition and subtraction. The advantage is with closed populations in most studies of a causative factor.

POPULATIONS OF PATIENTS. The most satisfactory population of patients includes all recognized cases within a prescribed universe of time and space, with chance variation in severity, extent of involvement, duration of illness and the characteristics imposed by biological and social differences among people. Complete representation depends upon the extent to which other

than clinical methods extend recognition to the preclinical.

Necessity, or the advantage to a particular investigation, commonly decides that a portion of the general universe of patients is taken as the unit of study. Deaths frequently form the study group and because of the nature of coronary heart disease the more selected unit of those dying suddenly. In both instances restriction may extend to those necropsied.

Whether accumulated from private practice, from outpatient clinics, or from hospitals, populations of patients have the common limitation of an indefinite knowledge of the basic population to which they relate and how representative they are of the general universe of patients with the disease.

GENERAL POPULATIONS. In few situations does a general population, the whole of an identified universe, serve practically in field study. Most investigations require consent of individuals to participate, with the result that refusal introduces selection and question of the sample as representative of the whole.

For practical reasons concerned with availability, or consent, or ease of operations, selected fractions of a general population often serve as the study unit. Groups of employees within an industry, men in military service, participants in industrial insurance or pension or medical care schemes, school children, residents of institutions, and members of fraternal or other social groups[172] illustrate such populations. Selection is sometimes outspoken in such elementary characteristics as age, sex or race. A hidden individuality may rest in differences in risk, social behavior or environment. How representative it is of the general population from which it is drawn, and of the particular class it represents are invariable considerations.

POPULATION SIZE. Size of population ranks with kind in the design of field studies. Decision depends upon the particular circumstance, with time, the frequency of the event under observation and the desired degree of confidence the determining factors. Reasonable assumptions drawn from experience permit mathematical determination of numbers needed. The statistical result is corrected by consideration of epidemiological factors to assure a population size giving a satisfactory answer and yet avoiding wasted effort. A little early effort with yellow paper is cheaper than field operations as a means to gain this information, and also more assuring.

Sources of Information. The kind of population, the hypothesis to be tested and the study design determine the sources of information for a particular study. For patient populations, the records of medical examination are those of original and progress observations. Such populations serve most usefully as a fixed population followed by life table methods. Clinical records accordingly require supplement by periodic interview or questionnaire, with the first definitely preferred.

Necropsy records of a teaching hospital[36] are the usual source of information for studies of deaths. Those of medical examiners have special usefulness in coronary heart disease; comparison between localities is possible where legal requirements and practices are similar. All deaths are highly selected in terms of the universe of patients with coronary heart disease and of course the general population. Nevertheless, as a source of material for epidemiological purposes necropsy records have not had full use in this or any other chronic disease.

The recorded data of the National Office of Vital Statistics provide the material for study of deaths from coro-

nary heart disease in relation to a general population, with census data providing the denominator for rates. Epidemiologic usefulness is restricted by the necessary limitation of analyses to the standard demographic variables provided, and for coronary heart disease especially by the vagaries of classification.

Sources of morbidity information for general populations are either the existing records ordinarily collected by community groups for other purposes, or data obtained by direct field investigation. Health records of selected industries are in the first group, as are insurance statistics, particularly of industrial policyholders. A heart register patterned after the cancer register does not exist nor is coronary heart disease justifiably reportable. Routine records or even those of the general health survey[154] commonly fail to provide the detailed information or individual items about coronary heart disease essential to evaluation of a suspected causative factor. A field study directed to the particular purpose becomes necessary.

Ad Hoc Studies. Cross section measurement of frequency is the determination of prevalence. All cases of coronary heart disease, old and new, all forms, and of varying duration, are enumerated at a specified time and rates calculated on the basis of a known population. Appropriate subdivisions of the population according to demographic, biologic and social characteristics result in specific frequency rates, for the disease as a whole and for its recognizable parts.

The field review or incidence study determines the rate at which new cases occur in the study population within specified intervals of time. This longitudinal pattern continued over a number of years is suited to chronic diseases. Short term design of the nature of a pilot study, or even prevalence investigation, sometimes suffices to establish causative factors; the usual contribution is recognition of leads to be developed by special investigation.

The long-term study takes two forms, retrospective and prospective; less commonly, a combination of the two. The distinction rests in that data are collected by working either backward or forward from an arbitrary date. That the one deals with the past and the other with the future does not hold necessarily, although that is usual.

The retrospective study, also known as a proband study, ordinarily starts with a population of patients identified as having coronary heart disease. Controls are essential. Commonly they are drawn from patients of the same source but with an unrelated disease or injury, thus eliminating one feature of selection; persons in good health are an alternative. Test subject and control are matched for essential characteristics other than the disease in question, such as age, sex, social status, or other attribute dictated by the study. Some things cannot be matched at all and some approximations are inevitable. Antecedent events and behavior in the past history of controls and test subjects are compared. The method saves time and effort in identifying cases; it is especially suited to diseases of uncommon occurrence. The disadvantages are those of selection inherent in any patient population. Restriction in ability to generalize findings to the total population may be lessened by check against known epidemiologic constants of that population.

The prospective study starts at a fixed time and with an established population. Cohorts are defined in terms of usual characteristics and those incident to the particular hypothesis. What takes place thereafter is determined by observation at stipulated

intervals and usually over a predetermined time set by the experimental design. Problems of sampling enter strongly into choice of population in order to avoid selection and because generalization does not extend beyond the universe involved. Technically a study of the general population is the more difficult and far more expensive; such studies are indicated in heart disease; a start has been made[41]. For prospective study to be feasible, the disease must be relatively common, and coronary heart disease qualifies. Lesser expense and ease of operations are attractions of an industrial or insurance population contrasted to a general population. The fundamental objective in longitudinal studies is comparison of the same group at different times; comparison is possible with other groups at the same time if relevant characteristics are alike. In essence, observations are of the natural history of the disease. The challenge is to develop means for recognition of the earlier clinical manifestations, and with adequate laboratory aid, a concept of precursors. Prognosis, too, can be made measurable.

Irrespective of planned procedure or ultraorganization, a principle as old as epidemiology itself comes into play in any field study, the value of the isolated special situation. It cannot be planned for and yet the opportunity is not to be lost. Sometimes more is to be learned than from hundreds of ordinary cases. This is the sort of evidence that came from an army mess where two casual visitors ate a single meal. Subsequently both came down with typhoid fever at their individual home stations at the same time that an epidemic involved the far away mess. The association settled the origin of their own difficulty and that of the outbreak.

Experimental design of field studies commonly suffers from inclusion of too many questions. The ideal is a test of a single association, to judge a stated hypothesis. The indiscriminate collection of information with a pious hope of ultimately finding out what was discovered marks the other extreme. No implication is made that a single field study is likely to settle the epidemiology of coronary heart disease. The structure of epidemiology rests on the interrelationship of many findings about a variety of factors and under a variety of circumstances. Knowledge of the natural history of a disease evolves through a framework of circumstantial evidence stronger than any of its parts.

The Direction of Research. The purpose of the earlier ecologic analysis was to gather possibilities for epidemiologic research in coronary heart disease. As so often happens, certain fundamental information emerges as the critical need in a forceful investigation of causes and an ultimate prevention.

The reliability of stated cause of death in coronary heart disease, a more useful classification of deaths and their place among causes of sudden death because of the related problems of atherosclerosis, are clinical and pathological obligations. Progress hinges in large part on the ability of laboratory investigators to develop a practical means for recognizing subclinical and earlier parts of the disease complex. Epidemiology has the particular charge to provide a quantitative idea of morbidity and mortality for the clinically definable coronary heart disease.

In the endeavor to identify causes, epidemiology does not stand alone, any more than do the other two major directions of research. Field observations require correlation with the contributions of clinic and laboratory, for fit in conclusions from common problems studied individually, for evidence derived by one method and not within the capabilities of another, and for leads suitable to development by

one or other procedure. This viewpoint has run throughout this review. Rather reasonably, active collaboration between disciplines is more frequent, particularly in the application of biochemical and nutritional research to field evaluation. Nutrition thereby is avoiding the situation[218] that arose in communicable disease practice around 1920 when interest in disease came close to disappearing in enthusiasm for the infectious agent.

The multiple causative factors in coronary heart disease make the problem of control an accomplishment of the future; today's challenge is that of research. However, the presence of multiple factors also has its advantages, for in working from mystery to mastery there is no need to wait upon one specific agent or the whole of causality. In other and analogous situations, understanding of a few components of the causative complex has resulted in a material advance in prevention; fluoridation of water supplies has accomplished much, although the causes of dental caries remain multiple, obscure and complex.

REFERENCES

(1) **Adlersberg, D., Parets, A. D.,** and **Boas, E. P.:** J. Am. Med. Assn., **141,** 246, 1949. (2) **Adlersberg, D., Schaefer, L. E.,** and **Wang, C.:** Science, **120,** 319, 1954. (3) **Ahrens, E. H., Jr., Tsaltas, T. T., Hirsch, J.,** and **Insull, W., Jr.:** J. Clin. Invest., **34,** 918, 1955. (4) **Altschul, R.:** Geriatrics, **10,** 208, 1955. (4a) **Amadeo, J. A.:** Bol. Asoc. Med. de Puerto Rico, **37,** 161, 1945. (5) American Heart Association: Diseases of the Heart and Blood Vessels: Facts and Figures. New York: American Heart Assn., 1954. (6) **Anderson R. J.,** and **Zukel, W. J.:** Dis. Chest, **24,** 278, 1953. (7) **Andrus, S. B., Mann, G. V., Fillios L. C.,** and **Stare, F. J.:** Fed. Proc., **15,** 542, 1956. (8) **Anitschkow, N.:** Experimental Arteriosclerosis in Animals, in Arteriosclerosis, ed. **E. V. Cowdry,** New York: Macmillan Co., 1933. (9) **Aschoff, L.:** Brit. Med. J., **2,** 1131, 1932. (10) Association for Research in Nervous and Mental Disease; Research Publication: Life Stress and Bodily Disease. Baltimore: Williams & Wilkins, 1950, vol. **29,** pt. 10.

(11) **Babbott, J. G., Babbott, F. L., Jr.,** and **Gordon, J. E.:** Am. J. Med. Sci., **231,** 338, 1956. (12) **Bake , G.:** An Essay Concerning the Cause of the Endemial Colic of Devonshire, London, College of Physicians, 1814. (13) **Barr, D. P., Russ, E. M.,** and **Eder, H. A.:** Tr. Assn. Am. Phys., **65,** 102, 1952, discussion, p. 108. (14) **Bauer, J.:** Constitution and Disease. New York: Grune & Stratton, 1945. (15) **Bean, W. B.,** and **Mills, C. A.:** Am. Heart J., **16,** 701, 1938. (16) **Beck, H. G.,** and **Suter, G. M.:** J. Am. Med. Assn., **110,** 1982, 1938. (17) **Beveridge, J. M. R., Connell, W. F.,** and **Mayer, G. A..** Canad. J. Biochem. and Physiol., **34,** 441, 1956. (18) **Billings, F. T., Jr., Kalstone, B. M., Spencer, J. L., Ball, C. O. T.,** and **Meneely, G. R.:** Am. J. Med., **7,** 356, 1949. (19) **Block, W. J., Barker, N. W.,** and **Mann, F. D.:** Circulation, **4,** 674, 1951. (20) **Block, W. J., Crumpacker, E. L., Dry, T. J.,** and **Gage, R. P.:** J. Am. Med. Assn., **150,** 259, 1952. (21) **Blumgart, H. L., Freedberg, A. S.,** and **Kurland, G. S.:** Circulation, **1,** 1105, 1950. (22) **Blumgart, H. L., Schlesinger, M. J.,** and **Davis, D.:** Am. Heart J., **19,** 1, 1940. (23) **Boas, E. P.,** and **Epstein, F. H.:** A.M.A. Arch. Int. Med., **94,** 94, 1954. (24) **Brock, J. F.,** and **Bronte-Stewart, B.:** Minnesota Med., **38,** 852, 1955. (25) **Bronte-Stewart, B., Eales, L., Antonis, A.,** and **Brock, J. F.:** Lancet, **1,** 101, 1956. (26) **Bronte-Stewart, B.,** and **Heptinstall, R. H.:** J. Path. & Bact., **68,** 407, 1954. (27) **Bronte-Stewart, B., Keys, A., Brock, J. F., Moodie, A. D., Keys, M. H.,** and **Antonis, A.:** Lancet, **2,** 1103, 1955. (28) **Brown, R. K., Boyle, E.,** and **Anfinsen, C.:** J. Biol. Chem., **204,** 423, 1953. (29) **Bunting, C. H.,** and **Bunting, H.:** A.M.A. Arch. Path., **55,** 257, 1953. (30) **Byers, S. O.,** and **Friedman, M.:** Am. J. Physiol., **179,** 79, 1954.

(31) **Cannon, W. B.,** and **Mendenhall, W. L.:** Ibid., **34,** 225, 232, and 241, 1914. (32) **Chandler, H. L.,** and **Mann, G. V.:** New England J. Med., **249,** 1045, 1953. (33) **Chapman, I., Goldbloom, A. A., Mirrer, G.,** and **Eiber, H. B.:** A.M.A. Arch. Path.,

61, 357, 1956. (**34**) **Chernick, S., Srere, P. A.,** and **Chaikoff, I. L.:** J. Biol. Chem., **179**, 113, 1949. (**35**) **Clark, E. G.,** and **Morsell, J. A.:** Am. J. Pub. Health, **42**, 542, 1952. (**36**) **Clawson, B. J.:** Am. Heart J., **22**, 607, 1941. (**37**) **Connell, W. F.:** Canad. Med. J., **70**, 248, 1954. (**38**) **Cook, D. L., Mills, L. M.,** and **Green, D. M.:** J. Exper. Med., **99**, 119, 1954. (**39**) **Cook, R. P.,** and **McCullagh, G. P.:** Quart. J. Exper. Physiol., **29**, 283, 1939.

(**40**) **Dauber, D. V.,** and **Katz, L. N.:** A.M.A. Arch. Path., **36**, 473, 1943. (**41**) **Dawber, T. R., Meadors, G. F.,** and **Moore, F. E.:** Am. J. Pub. Health, **41**, 279, 1951. (**42**) **Dedichen, J., Strom, A., Adelsten-Jensen, R.,** and **Closs, K.:** Tr. Josiah Macy, Jr. Foundation, **5**, 117, 1951. (**43**) **Dock, W.:** (a) J. Am. Med. Assn., **131**, 875, 1946; (b) Tr. Josiah Macy, Jr. Foundation, **5**, 129, 1951. (**44**) **Dolger, H.:** Factors Influencing Premature Cardiovascular Degeneration in Diabetes Mellitus in Progress in Clinical Endocrinology, New York: Grune & Stratton, 1950. (**45**) **Doll, R.,** and **Hill, A. B.:** Brit. Med. J., **1**, 1451, 1954. (**46**) **Doyle, J. T., DeLalla, L. S., Baker, W. H., Heslin, A. S.,** and **Brown, R. K.:** J. Clin. Invest., **35**, 699, 1956. (**47**) **Dublin, T. D.:** Personal communication, 1956. (**48**) **Duff, G. L.,** and **McMillan, G. C.:** Am. J. Med., **11**, 92, 1951. (**49**) **Duguid, J. B.:** (a) Lancet, **1**, 891, 1954; (b) Practitioner, **175**, 241, 1955. (**50**) **Dunlop, D. M.:** Brit. Med. J., **2**, 383, 1954.

(**51**) **Eder, H. A.:** Plasma Lipoproteins in Atherosclerosis and Related Diseases, in Symposium on Atherosclerosis, Washington, D. C., National Acad. Sci., National Res. Counc., 1955. (**52**) Editorial: (a) Lancet, **2**, 1123, 1955; (b) New England J. Med., **254**, 1044, 1956. (**53**) **Engelberg, H., Kuhn, R.,** and **Steinman, M.:** Circulation, **13**, 489, 1956. (**54**) **Enos, W. F., Holmes, R. H.,** and **Berger, J.:** J. Am. Med. Assn., **152**, 1090, 1953. (**55**) **Epstein, F. H.,** and **Boas, E. P.:** J. Gerontol., **10**, 331, 1955. (**56**) **Euler, U. S.:** Adrenalin and Noradrenalin in Various Kinds of Stress, in Symposium on Stress, Washington, National Res. Counc., and Army Med. Serv. Grad. School, 1953.

(**57**) **Faber, M.:** A.M.A. Arch. Path., **48**, 342, 1949. (**58**) **Fangman, R. J.,** and **Hellwig, C. A.:** Am. J. Path., **23**, 901, 1947. (**59**) **Feldman, M.,** and **Feldman, M., Jr.:** Am. J. Digest. Dis., **22**, 1, 1955. (**60**) **Fillios, L. C., Andrus, S. B., Mann, G. V.,** and **Stare, F. J.:** Fed. Proc., **15**, 550, 1956. (**61**) **Fishberg, A. M.:** Hypertension and Nephritis, ed. 5, Philadelphia: Lea & Febiger, 1954. (**62**) **Frantz, I. D.:** Minnesota Med., **38**, 779, 1955. (**63**) **Fullerton, H. W., Davie, W. J. A.,** and **Anastasopoulos, G.:** Brit. Med. J., **2**, 250, 1953. (**64**) **Funkenstein, D. H., King, S. H.,** and **Drolette, M.:** Psychosom. Med., **16**, 404, 1954.

(**65**) **Garcia, P., Roderuck, C.,** and **Swanson, P.:** J. Nutrition, **55**, 601, 1955. (**66**) **Gardner, F. E.,** and **White, P. D.:** Ann. Int. Med., **31**, 1003, 1949. (**67**) **Gauld, R. L.,** and **Craig, J. P.:** Am. J. Hyg., **59**, 32, 1954. (**68**) **Gertler, M. M., Hudson, P. B.,** and **Jost, H.:** Geriatrics, **8**, 500, 1953. (**69**) **Gertler, M. M.,** and **Oppenheimer, B. S.:** Geriatrics, **9**, 157, 1954. (**70**) **Gertler, M. M.,** and **White, P. D.:** Coronary Heart Disease in Young Adults: a Multidisciplinary Study. Cambridge: Harvard University Press, 1954. (**71**) **Gilliam, A. G.:** Pub. Health Rep., **69**, 907, 1954. (**72**) **Gofman, J. W., Glazier, F., Tamplin, A., Strisower, B.,** and **DeLalla, O.:** Physiol. Rev., **34**, 589, 1954. (**73**) **Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A.,** and **Strisower, B.:** Circulation, **2**, 161, 1950. (**74**) **Gofman, J. W., Tamplin, A.,** and **Strisower, B.:** J. Am. Dietetic Assn., **30**, 317, 1954. (**75**) **Goldberger, J., Wheeler, G. A.,** and **Sydenstricker, E.:** J. Am. Med. Assn., **71**, 944, 1918. (**76**) **Gordon, J. E.:** (a) Am. J. Pub. Health, **39**, 504, 1949; (b) The Newer Epidemiology, in Tomorrow's Horizon in Public Health, New York, Pub. Health Assn. of New York City, 1950; (c) Ecological Investigation of Disease, in Research in Public Health, New York, Milbank Mem. Fund, 1952; (d) J. Royal San. Institute, **74**, 445, 1954. (**77**) **Gordon, J. E.,** and **Augustine, D. L.:** Am. J. Med. Sci., **216**, 343, 1948. (**78**) **Gordon, J. E.,** and **le Riche, H.:** Ibid., **219**, 321, 1950. (**79**) **Gordon, J. E., O'Rourke, E., Richardson, F. L. W., Jr.,** and **Lindemann, E.:** Ibid., **223**, 316, 1952. (**80**) **Gordon, I.:** Med. Officer, **94**, 256, 1955. (**81**) **Graybiel, A., Starr, R. S.,** and **White, P. D.:** Am. Heart J., **15**, 89, 1938. (**82**) **Gross, L., Epstein, E. Z.,** and **Kugel, M. A.:** Am. J. Path., **10**, 253, 1934. (**83**) **Grüner, A., Hilden, T., Raaschou, F.,** and **Vogelius, H.:** Am. J. Med., **14**, 433, 1953.

(**84**) **Hahn, P. F.:** Science, **98**, 19, 1943. (**85**) **Hammon, W. M.:** Am. J. Trop. Med., **28**, 515, 1948. (**86**) **Hammond, E. C.,** and **Horn, D.:** J. Am. Med. Assn., **155**,

1316, 1954. (87) **Henderson, C. B.**: Brit. Heart J., **15**, 278, 1953. (88) **Herbst, F. S. M., Lever, W. F.,** and **Waddell, W. R.**: Science, **123**, 843, 1956. (89) **Herrick, J. B.**: J. Am. Med. Assn., **59**, 2015, 1912. (90) **Herzstein, J., Wang, C. I.,** and **Adlersberg, D.**: Ann. Int. Med., **40**, 290, 1954. (91) **Hewitt, J. E., Hayes, T. L., Gofman, J. W., Jones, H. B.,** and **Pierce, F. T.**: Am. J. Physiol., **172**, 579, 1953. (92) **Heyer, H. E., Teng, H. C.,** and **Barris, W.**: Am. Heart J., **45**, 741, 1953. (93) **Hindhede, M.**: J. Am. Med. Assn., **74**, 381, 1920. (94) **Horita, A.,** and **Loomis, T. A.**: J. Exper. Med., **100**, 381, 1954. (95) **Hueper, W. C.**: (a) A.M.A. Arch. Path., **38**, 162, 245, 350, 1944; (b) Ibid., **39**, 51, 117, 187, 1945. (96) **Hunter, D.**: The Diseases of Occupations. Boston: Little, Brown & Co., 1955.

(97) **James, G.,** and **Hilleboe, H. E.**: Am. J. Pub. Health, **45**, 140, 1955. (98) **Joslin, E. P., Root, H. F., White, P.,** and **Marble, A.**: The Treatment of Diabetes Mellitus. Philadelphia: Lea & Febiger, 1952.

(99) **Katz, L. N.,** and **Stamler, J.**: Experimental Atherosclerosis. Springfield: Charles C Thomas, 1953. (100) **Katz, L. N., Stamler, J.,** and **Pick, R.**: J. Am. Med. Assn., **161**, 536, 1956. (101) **Keil, P. G.,** and **McVay, L. V., Jr.**: Circulation, **13**, 712, 1956. (102) **Keys, A., Anderson, J. T., Fidanza, F., Keys, M. H.,** and **Swahn, B.**: Clinical Chemistry, **1**, 34, 1955. (103) **Keys, A., Fidanza, F., Scardi, V.,** and **Bergami, G.**: Lancet, **2**, 209, 1952. (104) **Keys, A., Fidanza, F., Scardi, V., Bergami, G., Keys, M. H.,** and **DiLorenzo, F.**: A.M.A. Arch. Int. Med., **93**, 328, 1954. (105) **Keys, A., Vivanco, F., Rodriguez, M. J. L., Keys, M. H.,** and **Castro, M. H.**: Metabolism, **3**, 195, 1954. (106) **Kinsell, L. W.,** and **Michaels, G. D.**: Fed. Proc., **14**, 661, 1955. (107) **Kinsell, L. W., Michaels, G. D.,** and **Foreman, N.**: Geriatrics, **10**, 67, 1955. (108) **Kunkel, H. G.,** and **Slater, R. J.**: J. Clin. Invest., **31**, 677, 1952. (109) **Kurland, L. T.**: Am. J. Hyg., **55**, 457, 1952.

(110) **Larsen, N. P.**: Hawaii Med. J., **14**, 485, 1955. (111) **Leach, W. B.**: Canad. Med. Assn. J., **73**, 733, 1955. (112) **Leary, T.**: (a) Bull. New York Acad. Med., **17**, 887, 1941; (b) A.M.A. Arch. Path., **32**, 507, 1941. (113) **Lee, K. T.,** and **O'Neal, R. M.**: A.M.A. Arch. Surg., **72**, 622, 1956. (114) **Lee, K. T.,** and **Thomas, W. A.**: (a) A.M.A. Arch. Path., **60**, 616, 1955; (b) A.M.A. Arch. Int. Med., **97**, 421, 1956. (115) **Levene, C. I.**: Lancet, **2**, 1216, 1955. (116) **Liebow, I. M., Hellerstein, H. K.,** and **Miller, M.**: Am. J. Med., **18**, 438, 1955. (117) **Lindsay, S., Skahen, R.,** and **Chaikoff, I. L.**: A.M.A. Arch. Path., **61**, 207, 1956. (118) **Lober, P. H.**: Ibid., **55**, 357, 1953. (119) **Lyon, T. P., Yankley, A., Gofman, J. W.,** and **Strisower, B.**: California Med., **84**, 325, 1956.

(120) **Malinow, M. R., Hojman, D.,** and **Pellegrino, A. A.**: A.M.A. Arch. Path., **61**, 11, 1956. (121) **Malmros, H.**: Acta med. Scandinav., Suppl., **246**, 137, 1950. (122) **Mann, G. V., Andrus, S. B., McNally, A.,** and **Stare, F. J.**: J. Exper. Med., **98**, 195, 1953. (123) **Mann, G. V., Munoz, J. A.,** and **Scrimshaw, N. S.**: Am. J. Med., **19**, 25, 1955. (124) **Mann, G. V., Nicol, B. M.,** and **Stare, F. J.**: Brit. Med. J., **2**, 1008, 1955. (125) **Mann, G. V. Teel, K., Hayes, O., McNally, A.,** and **Bruno, D.**: New England J. Med., **253**, 349, 1955. (126) **Master, A. M.**: Circulation, **8**, 170, 1953. (127) **Master, A. M., Jaffee, H. L.,** and **Chesky, K.**: J. Am. Med. Assn., **153**, 1499, 1953. (128) **Mayer, J.**: Physiol. Rev., **33**, 472, 1953. (129) **McDevitt, E.,** and **Wright, I. S.**: The Cardiovascular System, in **Wynder, E. L.**: The Biologic Effects of Tobacco, Boston: Little, Brown and Co., 1955. (130) **Means, J. H.**: The Thyroid and Its Diseases, 2nd ed., Philadelphia: J. B. Lippincott Co., 1948. (131) **Miles, H. H. W., Waldfogel, S., Barrabee, E. L.,** and **Cobb, S.**: Psychosom. Med., **16**, 455, 1954. (132) **Mills, C. A.**: South Dakota J. Med. and Pharm., **1**, 91, 1948. (133) **Minkowski, W. L.**: Am. J. Med. Sci., **214**, 623, 1947. (134) **Mönckeberg, J. G.**: Klin. Wchnschr., **3**, 1473, 1521, 1924. (135) **Monroe, R. T.**: Diseases in Old Age: A Clinical and Pathological Study of 7,941 Individuals over 61 Years of Age, Cambridge: Harvard University Press, 1951. (136) **Moon, H. D.,** and **Rinehart, J. F.**: Circulation, **6**, 481, 1952. (137) **Morris, J. N.**: Lancet, **1**, 69, 1951. (138) **Morris, J. N.,** and **Heady, J. A.**: Brit. J. Indust. Med., **10**, 245, 1953. (139) **Morris, J. N., Heady, J. A., Raffle, P. A. B., Roberts, C. G.,** and **Parks, J. W.**: Lancet, **2**, 1053, 1111, 1953. (140) **Morrison, L. M.**: J. Am. Med. Assn., **159**, 1425, 1955. (141) **Moschcowitz, E.**: Ibid., **90**, 733, 1928. (142) **Moskowitz, M. S., Moskowitz, A. A., Bradford, W. L., Jr.,** and **Wissler, R. W.**: A.M.A. Arch. Path., **61**, 245, 1956.

(143) National Office of Vital Statistics: Vital Statistics of the United States, 1952. Washington: Government Printing Office, 1955. (144) **Necheles, H.**: Am. J. Digest. Dis., **18**, 8, 229, 1951. (145) **Newburgh, L. H.**, and **Clarkson, S.**: A.M.A. Arch. Int. Med., **31**, 653, 1923.

(146) **O'Brien, J. R.**: Lancet, **2**, 690, 1955. (147) **Oliver, M. F.**, and **Boyd, G. S.**: (a) Brit. Heart J., **15**, 387, 1953; (b) Minnesota Med., **38**, 794, 1955; (c) Brit. Heart J., **17**, 299, 1955. (148) **Ophüls, W.**: The Pathogenesis of Arteriosclerosis, in **Cowdry, E. V.**: Arteriosclerosis. New York: Macmillan Co., 1933. (149) **Osler, W.**: Lancet, **1**, 839, 1910.

(150) **Paterson, J. C.**: The Reaction of the Arterial Wall to Intra-Mural Hemorrhage, in Symposium on Atherosclerosis, Washington, D. C., National Acad. Sci., National Res. Council, 1954. (151) **Paterson, J. C., Cornish, B. R.**, and **Armstrong, E. C.**: Canad. Med. Assn. J., **74**, 538, 1956. (152) **Paterson, J. C., Slinger, S. J.**, and **Gartley, K. M.**: A.M.A. Arch. Path., **45**, 306, 1948. (153) **Peel, A. A. F.**: Brit. Heart J., **17**, 319, 1955. (154) **Perrott, G. St. J., Tibbitts, C.**, and **Britten, R. H. M.**: Pub. Health Rep., **54**, 1663, 1939. (155) **Petersen, W. F.**: Man–Weather–Sun, Springfield: Charles C Thomas, 1947. (156) **Phipps, C.**: J. Am. Med. Assn., **106**, 761, 1936.

(157) **Raab, W.**, and **Gigee, W.**: Circulation, **11**, 593, 1955. (158) **Rabson, S. M.**, and **Helpern, M.**: Am. Heart J., **35**, 635, 1948. (159) Report: Committee on Lipoproteins and Atherosclerosis, National Advisory Heart Council, 1956. (160) **Rinehart, J. F.**, and **Greenberg, L. D.**: Am. J. Path., **25**, 481, 1949. (161) **River, A. V.**, and **Dimitroff, S. P.**: Circulation, **9**, 533, 1954. (162) **Robinson, D. S.**: Biochem. J., **62**, 188, 1956. (163) **Roddis, L. H.**: James Lind: Founder of Nautical Medicine. New York: Henry Schuman, Inc., 1950. (164) **Rokitansky, C. J. W. P.**: Manual of Pathological Anatomy. London: The Sydenham Society, 1849–1854. (165) **Ross P. H.**, and **Ivy, A. C.**: Quart. Bull., Northwestern Univ. Med. School, **20**, 424, 1946. (166) **Roth, G. M.**: Tobacco and the Cardiovascular System; the Effects of Smoking and of Nicotine on Normal Persons. Springfield: Charles C Thomas. (167) **Russ, E. M., Eder, H. A.**, and **Barr, D. P.**: Am. J. Med., **11**, 468, 1951. (168) **Ryle, J. A.**, and **Russell, W. T.**: Brit. Heart J., **11**, 370, 1949.

(169) **Saphir, O.**, and **Gore, I.**: A.M.A. Arch. Path., **49**, 418, 1950. (170) **Saphir, O., Ohringer, L.**, and **Silverstone, H.**: Am. J. Med. Sci., **231**, 494, 1956. (171) **Sapping-ton, S. W.**, and **Cook, H. S.**: Am. J. Med. Sci., **192**, 822, 1936. (172) **Sartwell, P. E.**: Am. J. Pub. Health, **45**, 609, 1955. (173) **Schlesinger, M. J.**, and **Zoll, P. M.**: A.M.A. Arch. Path., **32**, 178, 1941. (174) **Schneider, R. A.**:The Relation of Stress to Clotting Time, Relative Viscosity and Certain Other Biophysical Alterations of the Blood in the Normotensive and Hypertensive Subject, in Life Stress and Bodily Disease. Baltimore: Williams & Wilkins Co., 1950. (175) **Schnur, S.**: (a) Ann. Int. Med., **39**, 1018, 1953; (b) Ibid., **44**, 476, 1956. (176) **Schroeder, H. A.**: J. Chron. Dis., **2**, 28, 1955. (177) **Sellers, E. A.**, and **You, R. W.**: Brit. Med. J., **1**, 815, 1956. (178) **Selye, H.**: J. Chron. Dis., **2**, 583, 1955. (179) **Sheldon, W. H.**: The Varieties of Human Physique. New York: Harper and Bros., 1940. (180) **Shepard, W. P.**, and **Marks, H. H.**: Minnesota Med., **38**, 736, 1955. (181) **Simms, H. S., Lindgren, F. T., Harmison, C. R., Nichols, A. V.**, and **Muraviev, T.**: Lab. Invest., **5**, 162, 1956. (182) **Sinclair, H. M.**: Lancet, **1**, 381, 1956. (183) **Smart, T. B.**, and **Bruce, R. A.**: Am. J. Med. Sci., **230**, 380, 1955. (184) **Smith, F. J., Keyes, J. W.**, and **Denham, R. M.**: Tr. Am. Clin. and Climatol. Assn., **62**, 202, 1950. (185) **Smith, T.**: Parasitism and Disease. Princeton: Princeton University Press, 1934. (186) **Snow, P. J. D., Jones, A. M.**, and **Daber, K. S.**: Brit. Heart J., **17**, 503, 1955. (187) **Spain, D. M., Bradess, V. A.**, and **Huss, G.**: Ann. Int. Med., **38**, 254, 1953. (188) **Stamler, J., Katz, L. N.**, and **Pick, R.**: Nutritional-Endocrinological Interrelationships in the Pathogenesis of Hypertension and Atherosclerosis Over the Life Span, in 4th Annual Report on Stress, ed. **H. Selye** and **G. Heuser**. Montreal: Acta, Inc., 1954. (189) **Stamler, J., Pick, R.**, and **Katz, L. N.**: (a) Circulation, **4**, 262, 1951; (b) Ibid., **10**, 251, 1954. (190) **Steiner, A.**, and **Domanski, B.**: A.M.A. Arch. Int. Med., **71**, 397, 1943. (191) **Steiner, A.**, and **Kendall, F.**: A.M.A. Arch. Path., **42**, 433, 1946. (192) **Strode, G. K.**: Yellow Fever. New York: McGraw-Hill Book Co., Inc., 1951. (193) **Strøm, A.**, and **Jensen, R. A.**: Lancet, **1**, 126, 1951. (194) **Stuckey, D.**: Med. J. Australia, **1**, 169, 1955. (195) **Surgenor, D. M.**: Extracellular Lipoproteins, in Symposium on Atherosclerosis. Washington, D. C.:

National Acad. Sci., National Res. Counc., 1955. (**196**) Symposium on Lipids in Nutrition: Fed. Proc., **14**, 639, 1955.

(197) **Taylor, C. B.**, and **Gould, R. G.**: Circulation, **2**, 467, 1950. (**198**) **Taylor, C. E.**, and **Gordon, J. E.**: Am. J. Med. Sci., **225**, 320, 1953. (**199**) **Taylor, H. E.**: Am. J. Path., **29**, 871, 1953. (**200**) **Texon, M.**: Personal communication to Dr. P. D. White, 1956. (**201**) **Thomas, C. B.**, and **Cohen, B. H.**: Ann. Int. Med., **42**, 90, 1955. (**202**) **Tobian, L.**: Minnesota Med., **38**, 784, 1955. (**203**) **Trulson, M. F., Miller, D. C., Stare, F. J.**, and **White, P. D.**: To be published.

(204) **Underahl, L. O.**, and **Smith, H. L.**: Proc. Staff Meet., Mayo Clin, **22–23**, 479,1947. (**205**) United States Public Health Service: Cardiovascular Disease; Data on Mortality, Prevalence and Control Activities, Public Health Service Publication No. 429, Washington, Government Printing Office, 1955.

(206) **Vogel, J.**: The Pathological Anatomy of the Human Body. Philadelphia: Lea & Febiger, 1847.

(207) **Waldron, J. M.**, and **Duncan, G. G.**: Am. J. Med., **17**, 365, 1954. (**208**) **Weiss, E.**: Geriatrics, **11**, 151, 1956. (**209**) **Weiss, M. M.**: Am. J. Med. Sci., **231**, 9, 1956. (**210**) **Weiss, M. M.**, and **Gray, W. R.**: Ibid., **227**, 186, 1954. (**211**) **Wessler, S., Cohen, S.**, and **Fleischner, F. G.**: New England J. Med., **254**, 413, 1956. (**212**) **White, P. D.**: (a) J. Am. Med. Assn., **152**, 303, 1953. (b) Clinical Surveys in Italy, 1954, in Proc. 2nd Internat. Cong. of Cardiology, Washington, D. C., 1954. New York: Paul B. Hoeber, Inc. (to be published); (c) Personal communication, 1956. (213) **White, P. D.**, and **Brasil, A.**: Tr. Am. Clin. and Climatol. Assn., **51**, 61, 1935. (**214**) **Wilens, S. L.**: (a) Am. J. Path., **19**, 293, 1943; (b) A.M.A. Arch. Int. Med., **79**, 129, 1947; (c) Am. J. Path., **27**, 825, 1951. (**215**) **Wilgram, G. F.**, and **Hartroft, W. S.**: Brit. J. Exper. Path., **36**, 298, 1955. (**216**) **Wilkerson, H. L. C.**, and **Krall, L. P.**: J. Am. Med. Assn., **135**, 209, 1947. (**217**) **Willis, G. C.**: (a) Canad. Med. Assn., **67**, 302, 1952; (b) Ibid., **70**, 1, 1954. (**218**) **Winslow, C.-E. A., Smillie, W. G., Doull, J. A.**, and **Gordon, J. E.**: The History of American Epidemiology. St. Louis: C. V. Mosby Co., 1952. (**219**) **Winternitz, M. C., Thomas, R. M.**, and **LeCompte, P. M.**: The Biology of Arteriosclerosis. Springfield: Charles C Thomas, 1938. (**220**) **Wissler, R. W., Ellert, M. L., Schroeder, M. A.**, and **Cohen, L.**: A.M.A. Arch. Path., **57**, 333, 1954. (**221**) World Health Organization: (a) Demographic Yearbook, 1955, New York, United Nations, 1956; (b) Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. 6th revision, vols. 1 and 2. Geneva, Switzerland, 1948 and 1949. (**222**) **Wuest, J. H., Jr., Dry, R. J.**, and **Edwards, J. E.**: Circulation, **7**, 801, 1953.

(223) **Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., Gesler, M. A.**, and **Wilcox, B. B.**: Am. Heart J., **36**, 334, 481, and 683, 1948.

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF MAY 15, 1956

Protein-bound Iodine in the Neuro- and Adeno-hypophysis. WILLIAM C. FOSTER, J. F. MCCLENDON, AND L. O. GILMORE* (Department of Physiology, Hahnemann Medical College). PBI determinations by the method of McClendon and Foster in pooled samples of whole chicken, dog and cat hypophyses revealed values higher than the PBI levels in many other tissues. Because of the large size of the bovine hypophysis it was possible to determine the tissue PBI in the adeno- and neuro-hypophyseal lobes of separate glands. Hypophyses were extirpated from adult cows and steers, placed in acidulated water, boiled for one minute, homogenized in a Waring Blendor, and centrifuged. The PBI determination was made upon the mince. The range of PBI in the adenohypophysis varied from 7.1 to 46.6 μg. per 100 gm. fresh weight of tissue, with a mean of 20.1 μg. In steers the range extended from 12.9 to 49.0 with a mean of 16.2 μg. The range of PBI in the neurohypophysis of cows varied from 30.0 to 215.0 μg. per 100 gm. fresh weight, with a mean of 104.2 μg., while in the steers a range from 41.0 to 123.0 was shown, with a mean of 74.9 μg. PBI in the neurohypophysis of the cow was found to be five times greater than in the adenohypophysis and four times as great in the steer. The authors believe PBI to indicate thyroid hormone, as distinct from diiodotyrosine, and these data indicate that approximately 80% total pituitary PBI is present in the neurohypophysis. Since the PBI in the neurohypophysis is greater than in the adenohypophysis it seems possible that storage of the thyroid hormone may take place in the former lobe, and in some obscure manner it may be released to stimulate TSH in the adenohypophysis.

Terpenoid Intermediates in the Biosynthesis of Cholesterol. FRANK DITURI, M.D. AND FLORAPEARL A. COBEY, PH.D. (Department of Biochemistry, University of Pennsylvania School of Medicine). A particle-free, aqueous extract of rat liver is described which can incorporate C-14-labeled acetate and β-hydroxy-β-methylglutarate (HMG) into squalene and cholesterol. Using this enzyme system with labeled acetate as a substrate, it was shown that the prior addition of squalene reduces the incorporation of substrate into cholesterol. When the carrier squalene was recovered, it was found to be radioactive. When biosynthetic C-14-squalene was incubated with the same enyzme system, it was found to be incorporated readily into cholesterol. A modification of the enzyme system was prepared which could incorporate C-14-labeled HMG into squalene but could no longer utilize acetate for squalene or cholesterol synthesis. To this system were added the ten carbon terpenes, geraniol and geranic acid. These were without effect on the biosynthesis of squalene. The addition of the fifteen carbon terpenes, farnesol

*This presentation was made possible by a grant from the National Heart Institute, U.S.P.H.S.

and farnesenic acid, markedly reduced the incorporation of HMG into squalene. The recovered farnesol contained no activity, but the farnesenic acid was significantly radioactive. Several compounds have been prepared which are structural modifications of the farnesenic acid molecule. These compounds have been found to inhibit squalene synthesis *in vitro*. They are now being studied as possible antimetabolites for the biosynthesis of cholesterol *in vivo*.

The Pathogenesis of Acute Necrotizing Hemorrhagic Pancreatitis: An Experimental Study. PAUL NEMIR, JR., M.D. AND DAVID L. DRABKIN, M.D. (From the Departments of Surgery of the School of Medicine and the Graduate School of Medicine and the Harrison Department of Surgical Research of the University of Pennsylvania). In previous experiments on dogs, the finding, by spectrophotometric analysis, of an abnormal hemin pigment not previously reported aided in the study of the pathogenesis of strangulation obstruction with gangrenous bowel. Efforts to reproduce *in vitro* a fluid demonstrating the abnormal absorption spectrum were successful when blood was incubated with activated pancreatic juice. Further studies revealed the pigment to be a hemin split from globin presumably by enzymatic digestion. The resulting mixture was extremely lethal. During this time studies on the etiology and pathogenesis of acute pancreatitis were in progress. Our experience confirmed the work of others in that large amounts of bile (12 to 15 ml.) could be forcefully injected into the pancreatic ducts of dogs without causing fatal pancreatitis. The results, following injection of the fluid resulting from enzymatic digestion of blood, and in which the abnormal absorption spectrum was present, were markedly different. Even though very small amounts (4 to 5 ml.) were gently injected into the duct, the animals became extremely toxic with marked elevation of the temperature, tachycardia, coma and death within 24 to 36 hours. Necropsy revealed a severe acute necrotizing hemorrhagic pancreatitis. We feel these studies confirm the pancreatitis. When blood remains in contact with activated pancreatic juice for a short time an extremely toxic substance is formed.

Mechanism of Action of N-allylnormorphine in Morphine-induced Respiratory Depression in Man. HERBERT WENDEL, M.D. AND CHRISTIAN J. LAMBERTSEN, M.D. (Laboratory of Pharmacology, University of Pennsylvania School of Medicine). Studies on the respiratory effect of N-allylnormorphine and morphine in man confirmed the paradoxical effects reported in the literature: Intensification by N-allylnormorphine of morphine depression as well as diminution was observed. Antagonistic and synergistic effectiveness depended upon the magnitude of the morphine effect with respect to the relative potency of N-allylmorphine as respiratory depressant. N-allylnormorphine depressed respiration half as much as morphine. The relationship between combined effect and separate effects of the drugs indicates that 88% of the N-allylnormorphine effect substituted for 76% of the morphine effect, and 24% of the morphine effect replaced 12% of the N-allylnormorphine effect. The relationship between the ratios of substituted effects and the ratio of the molecular weights of the drugs suggests that N-allylnormorphine is twice as potent in replacing morphine as morphine is in replacing N-allylnormorphine.

The different potencies (with respect to respiratory depression and to mutual displacement) indicate two processes involved in the drug action: 1) Combination with receptors, 2) the phar-

macological action proper. Taking account of this the mathematical formulation of competitive inhibition has been extended to a general form applicable to all competitive drug interactions. The equation

$$E_{AB} = 100 \frac{\epsilon_A k_A [A] + \epsilon_B k_B [B]}{1 + k_A [A] + k_B [B]}$$

describes the combined effect (E_{AB}) of drugs A and B in terms of their concentrations [A] and [B], receptor affinity constants k_A and k_B, and efficacy constants ϵ_A and ϵ_B. For respiratory depression the following values were experimentally determined: $k_{MO} = 1$, $k_{NB} = 2$, $\epsilon_{MO} = 1$, $\epsilon_{NB} = 0.4$. With these values the equation indicates that a morphine effect equal to the maximum effect of N-allylnormorphine (40% depression of respiration) is not altered by N-allylnormorphine, greater effects are antagonized, smaller ones are intensified. The same conditions apply to all morphine actions which are exerted, with less potency, by N-allylnormorphine ($\epsilon_{NB} < \epsilon_{MO}$). Morphine effects not shared by N-allylnormorphine ($\epsilon_{NB} = 0$) are invariably antagonized. Thus the theory explains the opposite effects of N-allylnormorphine on some morphine actions (for example, respiratory depression), as well as its consistent antagonism to others (for example, prevention of abstinence syndrome). On the same basis the discrepancies of N-allylnormorphine effects between animals and man are understandable.

BOOK REVIEWS AND NOTICES

BRAIN MECHANISMS IN DIACHROME. By WENDELL J. S. KRIEG, B.S. IN MED., PH.D., Professor of Anatomy, Northwestern University Medical School. Pp. 188; 55 ills. Evanston, Ill.: Brain Books, 1955. Price, $7.00 single, $6.00 for ten or more copies.

DR. KRIEG has attempted a "vivid" three dimensional visualization of the nervous system at work, as it progresses through animals and culminates in man.

The author has written his text chiefly around his diachrome reconstruction of the human brain.

This review cannot do justice to this "little original atlas," printed in full color and included as a separate booklet. With this neuroanatomical diorama constantly before him, while reading the main text, the reader obtains a kinetic three dimensional picture of the cerbral components in their proper relation to each other.

Due to the small size of the book, the author has intentionally omitted details of structure of neurone, nerves and neuroglia given fully in histology textbooks, as well as blood vessels, meninges and many gross anatomical structures found in anatomy books.

In this book, the author has attempted to give the cerebral cortex its proper significance and importance through a synthesis of our newer knowledge of its connection, the differentiation and architecture of its areas, and the results of localized stimulation of operation.

This work is original, stimulating and will be helpful and welcome to the medical students, physicians, specialists and all interested in cerebral structure and function. M. S.

HENRY FORD HOSPITAL SYMPOSIUM ON CARDIOVASCULAR SURGERY. STUDIES IN PHYSIOLOGY, DIAGNOSIS AND TECHNIQUES. Edited by CONRAD R. LAM, M.D., Surgeon-in-Charge, Division of Thoracic Surgery, Henry Ford Hospital, Detroit. Pp. 543; 368 ills. Philadelphia and London: W. B. Saunders Company, 1955. Price, $12.75.

THIS volume contains the material presented during a symposium on the subject of cardiovascular surgery, held at the Henry Ford Hospital during the summer of 1954 and attended by an international group of authorities. The major purpose of the meeting was to provide an opportunity for the presentation of really new and perhaps controversial work. One day was spent on the problems of congenital heart disease, another on acquired heart disease, and a half day on surgery of the aorta and other arteries. Surgical procedures for coronary disease were omitted. The transcription of the proceedings has been well edited and presented in an attractive volume replete with an abundance of illustrations. While developments in surgical technique constitute a fair share of the volume, there is a splendid admixture of material dealing with pathophysiology and diagnostic procedures. Especially to be recommended is a series of four papers relative to adjustments between the systemic and pulmonary circulations. Much of the pertinent discussion of each of the papers given at the entire symposium is included in the transcription. The only disappointment in the whole book to the reviewer is the chapter in which the late results of mitral commissurotomy are discussed. The reader will be impressed by the crying need for more critical analyses eliminating the aura of enthusiasm and fervor surrounding the drama of cardiac surgery before many of the most important questions can be answered. A great deal is said concerning the criteria to be relied upon for predetermining the poor results, but there is little concerning the means used postoperatively to certify that the result has been a good and lasting one.

This objection, however, does not detract greatly from the value of the book as a whole and it is highly recommended to all cardiologists and internists. T. D.

CARDIAC ANOMALIES. A CLINICOPATHOLOGIC CORRELATION. By V. MORAGUES, M.D., Associate Professor of Pathology, Creighton University School of Medicine, and C. P. LYNXWILER, M.D., Assistant Professor of Pediatrics, St. Louis University School of Medicine. Pp. 92; 157 ills. Baltimore: The Williams & Wilkins Co., 1954. Price, $6.50.

THIS book presents a series of representative cases of congenital heart disease in which the diagnosis has been proven either by surgery or by necropsy. These are grouped under seven headings: Malpositions of the Heart, Defects of the Cardiac Septa, Valvular Anomalies, Anomalies of Septation of Truncus Arte-

riosus, Transposition Complexes, Anomalies of the Aortic Arch and Ebstein's Malformation of the Tricuspid Valve. There are a large number of excellent photographs of pathological specimens together with electrocardiograms, roentgenograms and brief summaries of the usual findings in each condition. In many instances diagrams are also included. A unique feature is the presentation of microphotographs of the lungs and great vessels illustrating the important changes produced in these structures. Only one contrast roentgen study is included and there is nothing concerning findings on catheterization. The viewpoint is definitely that of the anatomist rather than of the physiologist. The beginner in the study of congenital heart disease will therefore have great difficulty in achieving proper orientation. Under defects of the ventricular septum, for example, the statement is made that the prognosis is excellent unless pulmonary hypertension develops, but there is nothing said about why pulmonary hypertension is present in some cases. (Also no mention is made in this connection of the most serious threat to prognosis, bacterial endocarditis). Why microcytic anemia is included as one of the clinical features of auricular septal defect is a mystery. This book might be of some value as a supplement to good texts on the subject of congenital heart disease, but it has little else to commend it. T. D.

Asclepiades: His Life and Writings. A translation of Cocchi's Life of Asclepiades and Gumpert's Fragments of Asclepiades by Robert Montraville Green, M.D. Edited by Sidney Licht. Pp. 167. New Haven: Elizabeth Licht (360 Fountain Street), 1955. Price, $6.00.

This book contains translations of two works on Asclepiades by R. M. Green, the distinguished Harvard anatomist and writer, who died in May, 1955. Antonio Cocchi's "Life of Asclepiades" had appeared in an inferior English translation in 1762. Green's translation, from C. G. Gumpert's "Fragments from Asclepiades of Bithynia" (published at Weimar in 1794) here appears in English for the first time; in fact, the editor states that no book of Asclepiades has been published since 1841. Whether or not Asclepiades was the most important physician between Hippocrates and Galen, he was a valuable link in the chain of Greek medicine, as well as having apparently made various important original observations. As none of his writings have been preserved in their primary form, it is especially desirable to have these two works, which are extremely rare in the original, now available in English. E. K.

Counseling in Medical Genetics. By Sheldon C. Reed, Director, Dight Institute for Human Genetics, The University of Minnesota. Pp. 268. Philadelphia: W. B. Saunders Co., 1955. Price, $4.00.

Most physicians have had little training in medical genetics and are usually unable to give professional service in this area. It is the purpose of this book to supply enough background and information to aid the practicing physician to answer his patients' questions concerning heredity. For practical reasons only those traits which appear with a frequency of better than one in one thousand births are considered in detail, while rarer traits are listed in the appendix. The material is simply, clearly, and concisely presented.

This book is recommended as an excellent introduction to the field of medical genetics. C. Z.

Lehrbuch der Allgemeinen Psychopathologie. By Dr. Med. K. W. Bash. Mit einem Vorwort von Prof. H. Binder und einem Beitrag von H. Ladolt. Pp. 288; 10 ills. Stuttgart: Georg Thieme Verlag, 1955. (International Medical Book Corp., New York, U. S. Agents). Price, DM 29.50.

A textbook of psychopathology must, at the present stage, be based on a subjective selection of both facts and system. The writer on psychopathology finds himself in a situation much more similar to that of the historian than that of a scientist who can rely on a generally accepted system to which he has to add only some new viewpoints, here and there.

Bash is critical of one of the most important of his predecessors, Karl Jaspers. He feels that he can give more than "an order (of the facts) on the bases of methodological thought." It is the conviction of this reviewer that Bash has not and could not offer something basically different from what was done by Jaspers. Bash's book contains, however, more references to experimental psychology, on the one hand, and, on the other, to clinical psychiatric observation. The latter trait accounts for easier reading, as the facts to which the theory applied are presented in a familiar way. The last part of the book makes use of the classifications in psychiatry

such as the acute exogenous reaction type, the organic psychosyndrome, the syndrome of localized disorder (Das umschriebene Storsyndrom). It may be doubted whether the short physiologically oriented chapter on the general adaptation syndrome (Hans Selye) contributes anything worthwhile in the context of psychopathology. These remarks should not, however, leave the reader with the impression that this book has little to offer; quite the contrary, the many vivid case histories enliven the system which Bash has chosen and make it an up-to-date introduction to the topic. W. E.

THE HORMONES: PHYSIOLOGY, CHEMISTRY AND APPLICATIONS. VOL. III. Edited by GREGORY PINCUS AND KENNETH V. THIMANN, Worcester Foundation, Shrewsbury, Massachusetts, and Harvard University, Cambridge, Massachusets. Pp. 1012. New York: Academic Press Inc., 1955. Price, $22.00.

VOLUME III appears some seven years after the publication of Volume II. The many new discoveries that have occurred during this period, particularly in regard to the posterior pituitary, neural hormones and pituitary-adrenal axis, make this volume in no way a supplement to Volumes I and II. In the light of newly acquired knowledge most of the subject material is presented in a considerably different perspective than in Volumes I and II.

The text is composed of fifteen chapters which are devoted primarily to the chemical nature, metabolism and physiologic actions of the various known hormones. They are authored by recognized investigators in the various areas covered.

The last chapter, comprising 56 pages, covers in an abbreviated fashion the common clinical endocrinopathies. B. C.

MODERN TRENDS IN BLOOD DISEASES. Edited by JOHN F. WILKINSON, M.D., M.Sc., PH.D., F.R.C.P., F.R.I.C., Director, Department of Haematology, Manchester Royal Infirmary. Pp. 359; 91 ills., and 2 color plates. New York: Paul B. Hoeber, Inc., 1955. Price, $12.00.

THIS volume consists of 15 chapters which deal with many of the important advances in hematology during recent years. Some of the topics included are: "Bone Changes and Blood Diseases," by D. L. Griffiths; "Dermatological Aspects of Blood Diseases," by J. H. T. Davies; "Studies on Iron Metabolism," by C. V. Moore and R. Dubach; "Blood Pigments and Porphyrins," by C. Rimington; "Hemolytic Anemia," by W. H. Crosby and W. Dameshek; and "Changes in the Fundus in Diseases of the Blood," by D. B. H. Dawson.

Hematologists, in particular, and internists, in general, will find much of interest in these discussions. C. Z.

DEMONSTRATION OF PHYSICAL SIGNS IN CLINICAL SURGERY. By HAMILTON BAILEY, F.R.C.S. (ENG.), F.A.C.S., F.R.S.E., Emeritus Surgeon, Royal Northern Hospital, London, assisted by ALLAN CLAIN, M.B., F.R.C.S. (ENG.), Senior Surgical Registrar, Royal Cancer Hospital, London. 12th ed. Pp. 456; 681 ills. Baltimore: The Williams & Wilkins Co., 1954. Price, $8.00.

THIS splendid volume has enjoyed such widespread and well-deserved popularity that a new edition scarce needs any introduction. The author has long decried the growing tendency to rely upon laboratory and other auxiliary reports for a diagnosis, and strongly emphasizes the importance of the history and physical examination. His book is intended to be a series of demonstrations, and hence is profusely illustrated. A large percentage of the illustrations are in color, and all are well chosen and clear. The brief textual material is well written, concise and very much to the point. It is a book that should be part of every physician's library. T. D.

OFFICE PROCEDURES. By PAUL WILLIAMSON, M.D. Pp. 412; illustrated. Philadelphia: W. B. Saunders Co., 1955. Price, $12.50.

THIS is an attractive book, written by a physician of obvious ability. It consists of fifteen sections, ranging from office procedures applicable to ear, nose and throat work to office roentgenology by the general practitioner. Doctor Williamson writes well and inserts personal comments frequently, which add considerably to reader interest. I feel that the sections on surgery are not detailed enough for use by a man who is not well versed in the subject. I also feel that a considerable number of the surgical procedures should not be considered as office surgery and should certainly not be carried out at any time by anyone who has not had considerable training and experience. This certainly applies to tendon repair, surgery of the subacromial bursa, and treatment of com-

plicated fractures. The section on proctology includes operative procedures which I do not feel should be considered as applicable to office treatment. The same attitude holds for repair of major injuries to nerves and blood vessels.

The book, despite its surgical deficiencies, contains a large amount of useful information and, I feel, deserves a place in the library of the busy general practitioner who is required to maintain his office as an active clinic because of the inaccessibility of hospital care.

H. C.

ORIGINS OF RESISTANCE TO TOXIC AGENTS. Edited by M. G. SEVAG, Department of Microbiology, University of Pennsylvania, ROGER D. REID, Head, Microbiology Branch, Office of Naval Research and ORR E. REYNOLDS, Director, Biological Science Division, Office of Naval Research, Department of the Navy, Washington. Pp. 471; illustrated. New York: Academic Press Inc., 1955. Price, $12.00.

THIS symposium which was held under the joint auspices of the Office of Naval Research and the University of Pennsylvania in Washington, in 1954, deals with the origin of drug resistance and related problems. The sessions were devoted to: 1) Resistance to Microbicides; 2) Resistance to Herbicides and Insecticides; 3) Tolerance and Addiction to Drugs and Alcoholism; 4) Resistance Factors, Infectious Agents, and Cancer Cells; and 5) Physiological, Chemical, and Genetic Viewpoints. In addition to the formal presentations, the valuable discussion and comment provoked by each paper are also included.

Although the proceedings of a number of other fine symposia have been published in recent years, few, if any, can match the combined educational and inspirational values of this one. All of the sections are superbly written, but the discussion entitled "Experiments in Microevolution," by R. W. Gerard is outstanding. Research workers in many areas of medicine will find this volume both stimulating and richly rewarding. C. Z.

GROUP PROCESSES. Edited by BERTRAM SCHAFFNER, M.D. Pp. 318; 40 ills. New York: Josiah Macy, Jr. Foundation, 1955. Price, $5.50.

THE book consists of six chapters and an appendix, all having to do with group processes. The emphasis is upon the study of animals, particularly in their mating and competitive behavior. Dr. Frank A. Beech of Yale presents the first chapter, pointing out that the growth of any living system is dependent on the interaction of both extrinsic and intrinsic factors.

The ethologist Nito Tinbergen and Conrad Lorenz give excellent accounts of their work which prove highly interesting. The ethological point of view concentrates on the interaction between the young animal and the environment rather than attempting either learning process or instinct *in vacuo*. Helen Blauvelt gives an interesting paper on the relationship of the new born goats to their mothers. This work is somewhat analogous to that of Spitz on human infants and is important in being an early experimental work in a very important field that relates both to ethology and to psychology.

The seminars are sponsored by the Josiah Macy, Jr. Foundation to which science needs to be indebted for recognizing a vital need of crossing semantic barriers, synthesizing knowledge and stimulating new work. The book is highly recommended for interesting reading, for broadening our concepts of environmental and instinctual interaction and as a demonstration of the value of seminars as a scientific method. O. E.

THE RELIEF OF SYMPTOMS. By WALTER MODELL, M.D., Associate Professor of Clinical Pharmacology, Cornell University Medical College. Pp. 450; 5 ills. Philadelphia and London: W. B. Saunders Company, 1955. Price, $8.00.

THE reviewer has for a long time wished that someone would write a book on the treatment of symptoms. He has, therefore, been well pleased to read this new volume which so adequately fulfills his wish. The author of the book states that "the modern physician deals with the symptom, using it as a guide to diagnosis, a map of the course of the disease, and as an index to the response to therapy, but he may be so respectful of it that he is unwilling to attack it directly." This is most certainly true, and there is a crying need for correction of the last in this series of attitudes if physicians are to serve their patients to the fullest extent possible. Dr. Modell's volume reflects a long experience as a participant in the Cornell Conferences on Therapy and his membership on its editorial board. It is addressed primarily to medical students and also to the younger graduates whose philosophy and habits of practice have not yet "set." Commencing with an excellent section of five chapters dealing

with Theory, it then follows with a series of chapters on the management of Pain, Anxiety, Insomnia, Gas, Constipation, Diarrhea, Loss of Appetite, Obesity, Palpitations, Edema, Dyspnea, Cough, Fever, Weakness and Fatigue, Nausea and Vomiting, Vertigo, Itch, Hiccups, Unconsciousness, Convulsions, Skeletal Muscle Spasm, Menstrual Disorders, Frequency and Dysuria, and, finally, Jaundice. There is a short third part entitled, "Council," which deals with Cortisone and the Masking of Symptoms. While there are points here and there to which some will take exception, such is bound to be the problem in any book of treatment, and does not in any way detract from the tremendous value of the book as a whole. It is highly recommended, and should be worthy of many editions.

T. D.

PRESENT-DAY PSYCHOLOGY. Edited by A. A. ROBACK, Emerson College. Pp. 995; illustrated. New York: Philosophical Library, 1955. Price, $12.00.

IN this massive volume, Roback attempts to present a comprehensive view of present-day psychology, with indications of past developments, and future trends. The chapters range from discussions of neurology to questions of religion and parapsychology. Because of the wide scope of such a book, and because of the diversity of the 40 contributors, all experts in their special fields, the work necessarily loses a certain unity. This the editor readily admits and partially corrects by supplying editorial notes before each chapter. The organization of the collective papers centers about five divisions: 1) Topical Departments, 2) Branches, 3) Dynamic and Clinical Psychology, 4) Methods, and 5) Psychological Borderlands and Humanistics.

Although most of the topical departments are included in the first section, one wonders at the omission of a chapter on theoretical or experimental aspects of learning and motivation. It seems that because of the importance of this subject in present-day psychology, this field deserves a complete chapter rather than brief mention here and there. Perhaps one of the most unusual chapters in Part II, Branches, is an account of military psychology. Dynamic and Clinical Psychology is quite extensively covered from the point of view of both diagnostics and therapy. The Methods section is extremely short and seems somewhat out of place. However, the presentation of some recent trends in method will prove to be of value to those familiar with method in psychology. The final section Psychological Borderlands and Humanistics deals with such topics as psychology of literature, of art, of aesthetics. Although this subject matter comes as a surprise in this type of symposium, it shows that the editor has had the coverage to deal with material, such as the psychology of values, the status of which is not clearly established but which may lead to fruitful research and progress. O. E.

NEW BOOKS

Proceedings of the Symposium on Chlorpromazine and Mental Health, held in Philadelphia, June, 1955, under the auspices of Smith, Kline and French Laboratories. Pp. 200; 14 ills. Philadelphia: Lea & Febiger, 1955. Price, $3.00.

THE effects of chlorpromazine on emotional disturbance was presented, both in ambulatory treatment as well as in hospitalized patients. Many leaders in the field spoke about the value of the drug in calming patients and making them amenable to hospital routine, less destructive, and in some instances, obviating the need for lobotomy and reducing the necessity for electro shock treatment. The symposium had many different participants, from various parts of the country, who had used the drug over long periods. Their opinions and experience make worth while reading for the interested medical man.

The meeting ended with a dinner address by Dr. Winfred Overholser who found the drug useful at St. Elizabeth's Hospital and gave an optimistic evaluation of its potentialities.

O. E.

Multiple Sclerosis. BY DOUGLAS MCALPINE, M.D., F.R.C.P., NIGEL D. COMPSTON, M.A., M.D. (CANTAB), M.R.C.P., AND CHARLES E. LUMSDEN, M.D. (ABERD.). Pp. 304; 41 ills. London: E. & S. Livingstone, Ltd., 1955 (Williams & Wilkins Co., Baltimore, U. S. Agents). Price, $7.00.

THIS is an excellent and authoritative monograph by authors whose experience is wide. The subject is very thoroughly and completely covered in an encyclopedic manner. The reviewer is certain that no facet of multiple sclerosis has been neglected.

There are many case reports to illustrate the various points the authors wish to make. The authors' extensive experience is supplemented by the large bibliographies which appear at the end of each chapter. Reference is, of course, made to the references in the context.

The book was written in the hope that it will be of value to the physician and general practitioner and "may also encourage further work in this difficult field of research." It is too exhaustive for the general physician to use for other than a reference book and for that purpose it is superlative.

The chapter on treatment emphasizes the fact

which is so true, namely, that even though treatment is unsatisfactory the patient as a whole must have care and management and that preferably by others than charlatans.

The reviewer cannot recommend it too highly to those who have any interest in neurology in general and in multiple sclerosis in particular.

S. G.

NEW EDITIONS

The Doctors Mayo. By Helen Clapesattle. Pp. 484. New York: Pocket Books, Inc., 1956. Price, $.50.

This Pocket Books' edition meets a popular demand for a convenient sized volume of the biography of the founders of the Mayo Clinic. First published in 1941, the work was streamlined in 1954 to a more popular length and it is this second version which is here reprinted.

R. K.

The Diabetic Life: Its Control by Diet and Insulin. By R. D. Lawrence, M.D., Physician-in-Charge of Diabetic Department, King's College Hospital. 15th edition; Pp. 228; 27 ills. London: J. and A. Churchill, Ltd., 1955 (Little, Brown & Co., Boston, U.S. Agents). Price, $1.75.

This book presents the details of management of diabetes mellitus for the general practitioner and for the patient in a manner which permits both to use it effectively. For the physician, there are discussions dealing with routine management, special treatment procedures for surgical and other complications and details of treatment for juvenile and pregnant diabetics; for the patient, the particular chapters of importance are those dealing with diet, insulins and injection techniques and others devoted to various aspects of diabetic self-care. However, both physician and patient might profitably read the entire volume. The chapters on dietary methods may prove confusing to patients and physicians in the United States where the simplified Food Exchange Method is widely used.

C. S.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Published Monthly. Illustrated.

Subscription price: 1 year $10.00; 2 years $18.00.
(One year subscription to Canada, South and Central America, Philippines and Spain, $10.36; all other countries $11.14.)

All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

Manuscripts intended for publication in The American Journal of the Medical Sciences, and correspondence should be sent to the Editor:

Dr. Richard A. Kern, Temple University School of Medicine, Philadelphia 40, Pa.

Articles are accepted for publication in The American Journal of the Medical Sciences exclusively, except in the case of subsequent publication in Society proceedings.

Manuscripts should be typewritten on one side only, of good quality paper and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle.

Each article should have a summary which gives the essential point and purpose of the paper. This summary will be translated into Interlingua for the benefit of our foreign readers.

Illustrations accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. Line drawings and charts should be prepared with black India ink. Special arrangements can be made for printing color plates, elaborate tables or an excessive number of illustrations.

References should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

Return Postage should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 Reprints will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100. An order form showing cost of reprints is sent with proof. Individual reprints can usually be obtained by writing directly to the author.